JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

RISK OF SERIOUS NEUROPSYCHIATRIC ADVERSE EVENTS WITH CHANTIX (VARENICLINE TARTRATE)

BRIEFING DOCUMENT

05 September 2014

EXECUTIVE SUMMARY

On 8 April 2014, Pfizer submitted to the US Food and Drug Administration (FDA) a supplemental New Drug Application requesting updates to the CHANTIX® (varenicline tartrate) label to reflect currently available neuropsychiatric data from both clinical trial meta-analyses and published observational studies. On the basis of these new data, Pfizer requested that FDA remove the box around the warning regarding the risk of serious neuropsychiatric (NPS) events and update the content of the warning in the latter part of the label by adding information from the newly-available controlled clinical trials and observational studies. FDA subsequently scheduled a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the risk of serious neuropsychiatric adverse events with CHANTIX.

In July 2009, FDA added the boxed warning regarding serious neuropsychiatric events to the CHANTIX label, primarily on the basis of spontaneous adverse event reports. As FDA recognized in the CHANTIX label, because spontaneous reports are made voluntarily from a population of uncertain size and have other inherent limitations, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure based on them. Nonetheless, FDA and Pfizer recognized and evaluated the concerns raised by the spontaneous reports. At the time, FDA also indicated that the available clinical trial data – consisting of 10 placebo-controlled trials with 3,091 CHANTIX-treated patients, none of which were designed specifically to study patients with psychiatric illness – were not adequate either to rule in or rule out an association between suicidal behavior and the use of CHANTIX.[1] As of July 2009, there also were no large, population-based observational studies published that analyzed the neuropsychiatric safety of CHANTIX.

Since 2009, Pfizer has completed 8 additional CHANTIX smoking cessation clinical trials, for a current total of 18 randomized, placebo-controlled studies, which include 5,072 CHANTIX-treated subjects and 3,449 placebo-treated subjects. Of the 8 additional controlled clinical trials, 2 were conducted in subjects with past or current psychiatric disease – one in subjects with major depressive disorder (256 CHANTIX and 269 placebo subjects) (Section 5.3.2.1.1) and 1 in subjects with schizophrenia or schizoaffective disorder (84 CHANTIX and 43 placebo subjects) (Section 5.3.2.1.2). Of the 8 additional controlled clinical trials, 5 used the Columbia Suicide Severity Rating Scale (C-SSRS), which allowed more detailed evaluation of suicidal ideation and behavior using an appropriate standardized instrument. None of the individual trials showed any significant differences in the rates of serious neuropsychiatric adverse events or in the C-SSRS results between patients taking CHANTIX and those taking placebo.

In addition to results from the individual studies, Pfizer also conducted meta-analyses of the adverse events reported in the 18 available placebo-controlled clinical trials and of the C-SSRS results in the 5 placebo-controlled trials that employed the scale (Section 5.3.2.2). Within the 18-study meta-analysis of adverse events, with the exception of sleep disorders and disturbance, an acknowledged adverse reaction of varenicline, there were no consistent differences in neuropsychiatric event rates between varenicline and placebo. Likewise, in the

5-study meta-analysis of C-SSRS results, there were no significant differences between the rates of suicidal ideation and behavior in the 2 patient groups.

In addition, since 2009, independent researchers have conducted 4 large-scale, population-based observational studies comparing the neuropsychiatric safety of CHANTIX to nicotine replacement therapy (NRT) and/or bupropion. These studies provide an opportunity to examine a larger number of individuals exposed to CHANTIX in the real world, including patients with psychiatric illness. These studies, which are described in Section 5.3.3, also found that the rates of serious neuropsychiatric events in patients taking CHANTIX did not differ from those taking NRT or bupropion.

Against this backdrop, there are data indicating that CHANTIX is the single most effective smoking cessation therapy. In addition to consistent efficacy data generated from Pfizer-sponsored clinical trials, the Cochrane Group published a network meta-analysis, which showed that CHANTIX was significantly more effective than other approved monotherapies, as measured by sustained smoking cessation of at least 6 months from the start of treatment.

Timely communication of the newly acquired data is important because product labeling should accurately describe the benefits and risks of a product in order for patients and prescribers to make informed decisions about treatment. Used appropriately, boxed warnings can help to ensure that the use of a product with serious adverse reactions is restricted to those in whom the benefits clearly outweigh the risks. However, as presented in this Briefing Document, the totality of currently available data on the neuropsychiatric safety of CHANTIX, including meta-analyses of 18 placebo-controlled clinical trials and data from 4 large, population-based observational cohort studies comparing CHANTIX to other smoking cessation pharmacotherapies, do not show evidence of an increased risk of serious neuropsychiatric events with CHANTIX. The contemporary evidence is, therefore, inconsistent with a boxed warning.

The recommendation to monitor patients for the emergence of serious NPS adverse events associated with cessation of smoking can be appropriately communicated to prescribers in the Warnings and Precautions section of the CHANTIX label with revised wording that accurately describes the currently available evidence of risk.

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LIST OF ABBREVIATIONS

ACh	Acetylcholine
AE	Adverse event
ASR	Auditory startle response
BENESCO	Benefits of Smoking Cessation on Outcomes
BID	Twice daily
BIS-11	Barrett Impulsiveness Scale
BPRS	Brief Psychiatric Rating Scale
CA	Continuous abstinence
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CHD	Coronary heart disease
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
Cred I	Credible Interval
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
DB	Double blind
DSM-IV DSM-V	Diagnostic and Statistical Manual of Mental Disorders (4^{th} or 5^{th} Edition Text Revision)
EU	European Union
FDA	Food and Drug Administration
FST	Forced Swim Test
FTND	Fagerström Test for Nicotine Dependence
GABA	Gamma-aminobutyric acid
HAM-A	Hamilton Anxiety Rating Scale
hERG	Human ether-à-go-go related gene
HES	Hospital Episode Statistics
HLGT	(MedDRA) High Level Group Term
HLT	(MedDRA) High Level Term
HR	Hazard ratio
IC50	50% inhibitory concentration
IP	Intraperitoneal
IR	Incidence rate
Ki	Inhibition constant
LLT	(MedDRA) Lowest Level Term
MADRS	Montgomery Åsberg Depression Rating Scale
MAO-A	Monoamine oxidase-A
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHS	Military Health System
MNWS	Minnesota Nicotine Withdrawal Scale
N	Total number of subjects

n	Number of subjects in subset
NA	Not applicable
nAChR	Nicotinic acetylcholine receptor
NEC	Not elsewhere classified
NPS	Neuropsychiatric
NRT	Nicotine replacement therapy
OAS-M	Overt Aggression Scale-Modified
ONS	Office of National Statistics
OR	Odds ratio
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PHQ9	Patient Health Questionnaire-9
POMS	Profile of Mood States
PPI	Prepulse inhibition
PT	(MedDRA) Preferred term
QD	Once a day
RCT	Randomized, controlled trial
RD	Risk difference
REMS	Risk Evaluation and Mitigation Strategies
RR	Risk ratio
SAE	Serious Adverse Event
SC	Subcutaneous
SCID	Structured Clinical Interview for DSM Disorders
SMQ	Standardised MedDRA Query
SOC	(MedDRA) System Organ Class
SY	Subject-Years
TD	Treatment difference
TEAE	Treatment Emergent Adverse Event
TQD	Target Quit Date
UK	United Kingdom
US	United States
v	Version
VA	Veterans Affairs

LEXICON OF MedDRA TERMINOLOGY

All adverse event data presented in this document were coded using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a highly standardized medical terminology dictionary developed by the International Conference on Harmonization to facilitate international sharing of information regarding medicinal products with regulatory authorities.[2]

MedDRA Coding Hierarchy

There are five levels to the MedDRA coding hierarchy, arranged from very specific to very general and they include: Lowest Level Terms (LLTs), Preferred Terms (PTs), High Level Terms (HLTs), High Level Group Terms (HLGTs), and System Organ Classes (SOCs).

LLTs are the most specific level and these terms parallel how information is communicated and reflect how an observation might be reported in practice.

PTs are each a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic.

HLTs are groupings of related PTs based upon anatomy, pathology, physiology, etiology or function.

HLGTs are groupings of HLTs related to each other by anatomy, pathology, physiology, etiology or function.

SOCs are groupings of HLGTs based on etiology, manifestation site or purpose.

As an example: LLT=Suicide, PT=Completed suicide, HLT=Suicidal and self-injurious behavior, HLGT=Suicidal and self-injurious behaviors (not elsewhere classified), and SOC=Psychiatric disorders.

Standardized MedDRA Queries

Standardized MedDRA Queries (SMQs) are used to support signal detection and monitoring. SMQs are validated, standard sets of MedDRA terms. These sets of terms have undergone extensive review, testing, analysis and expert discussion by a working group of MedDRA and product safety experts. SMQs represent a variety of safety topics of regulatory interest. Some SMQs are a simple set of PTs while other SMQs are hierarchical containing subordinate SMQs. SMQs include narrow and/or broad terms. Narrow terms are those that are highly likely to represent the condition of interest.

1. INTRODUCTION

CHANTIX® (varenicline tablets) was approved by the United States (US) Food and Drug Administration (FDA) in May 2006 as an aid to smoking cessation treatment for adults 18 and over. It was the first non-nicotine prescription treatment specifically developed for smoking cessation approved in almost a decade which offered patients a unique and efficacious therapeutic approach to quitting smoking and represented an important new tool in the effort to reduce the significant health burden caused by cigarette smoking. There was a rapid uptake of CHANTIX in the US following its approval. As exposure to the product increased, information regarding its postmarketing use began to accumulate, including reports of serious NPS events. Beginning in November 2007, the CHANTIX label was revised several times to include and update a precaution and warning regarding serious NPS events, including suicidal ideation and behavior, reported during post-approval use of CHANTIX. In May of 2008, FDA requested a Risk Evaluation and Mitigation Strategies (REMS) for the product. The REMS includes a Medication Guide, and its goal is to inform patients about the potential risk of serious neuropsychiatric adverse events associated with the use of CHANTIX. The information regarding serious NPS events was further highlighted in a boxed warning added in the CHANTIX label in July 2009.

The boxed warning agreed upon by the Agency and Pfizer in July 2009 is shown below[3]:

> Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.
>
> All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.
>
> These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established.
>
> **Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal**

> **behavior.** In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.
> The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.
>
> (See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

The same information was also reflected in a warning under WARNINGS/Neuropsychiatric Symptoms and Suicidality in the CHANTIX label.

On 8 April 2014, based on the currently available data from both clinical trial meta-analyses and publically reported population-based observational studies, Pfizer submitted to FDA a supplemental New Drug Application requesting removal of the box around the warning regarding the risk of serious NPS events. Pfizer also proposed retaining under Warnings and Precautions the current warning regarding the risk of serious NPS events and updating it to reflect the currently available data.

FDA consequently scheduled a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the risk of serious NPS adverse events (AEs) with CHANTIX and agreed to the inclusion of information based on the new clinical and observational study data in the label, with subsequent review of data from Study A3051123 when available.

As presented in this Briefing Document, the accumulated data available to date concerning the NPS safety of CHANTIX, including larger meta-analyses of placebo-controlled clinical trials and data from large, population based observational cohort studies comparing varenicline to other smoking cessation pharmacotherapies, do not show evidence of an increased risk of serious NPS events with CHANTIX compared with other smoking cessation medications or placebo.

This Briefing Document reviews this safety data, as well as relevant data on the public health burden of tobacco and the efficacy of CHANTIX in smoking cessation treatment. Additionally, the potential public health impact of a reduction in utilization of the most effective smoking cessation aid is considered.

2. CHARACTERISTICS OF THE ADULT SMOKING POPULATION IN THE US

It is important to understand the smoking population in order to interpret data related to NPS events seen in smokers trying to quit.

Despite 50 years of efforts to reduce smoking since the 1st Surgeon General's report[4] on the harmful effects of tobacco, current estimates are that 42.1 million people, or 18.1% of all

adults (aged 18 years or older) in the US smoke cigarettes.[5] Smoking is prevalent across all adult demographic groups in the US. By gender, the prevalence in men is 20.5%, and in women, it is 15.8%. By age groups, it ranges from 8.9% of those 65 and older to 21.6% for those aged 25 to 44. By race or ethnicity, it ranges from 10.7% of Asians (non-Hispanic; excludes Native Hawaiians and Pacific Islanders) to 19.7% of Whites (non-Hispanic) to 21.8% of American Indians/Alaska Natives (non-Hispanic). By education level, it ranges from 5.9% of adults with a postgraduate college degree to 41.9% of adults with a GED diploma. By poverty status it is 17.0% for adults who live at or above the poverty level, while it is 27.9% for adults who live below the poverty level.[5]

Smoking is also more prevalent in people with current mental health concerns or problematic alcohol or illicit drug use. Several studies have shown that people with mental illnesses or illicit drug use are 2 to 3 times as likely to smoke as the general population.[6,7] The smoking prevalence for specific diagnosable disorders is: 59% for schizophrenia,[6,8,9] 44% for major depressive disorder (MDD),[6] 46%-60% for bipolar disorder,[10,11] and 43% for alcohol dependence[7]. Furthermore, mental illness and other addictions are more common in nicotine dependent smokers.[12] In a large US study, among nicotine-dependent individuals, 21.1% had a mood disorder, 22.0% had an anxiety disorder, 31.7% had a personality disorder, and 22.8% had an alcohol use disorder.

Of further concern, a number of studies have shown there is an association between smoking and suicide-related events.[13] In the US, the incidence of completed suicides is 12.7 per 100,000 people.[14] Lestikow et al[15], showed that smokers are 2.2 (95% CI: 1.0, 4.6) times more likely to commit suicide. In another study using a large, US population survey database (National Health Interview Survey), Lestikow et al[16] found that the absolute incidence rate of suicide by smoking status, expressed as suicides per 100,000 person-years, is lowest among never smokers (7.6), higher among former smokers (12.6) and highest among current smokers (23.3).

In Bolton et al's analysis of mental disorders and suicide attempts, individuals meeting criteria for nicotine dependence disorder were 1.42 (95% confidence interval [CI]: 1.16, 1.73) times more likely to have previously attempted suicide than those without the disorder suggesting that nicotine dependence is an important risk factor for suicide attempts. [17]

3. NICOTINE DEPENDENCE AND NICOTINE WITHDRAWAL

An understanding of nicotine dependence and withdrawal is also critical to interpreting NPS events seen in smokers trying to quit and to appreciating the mechanism of action of varenicline as described in Section 4.

3.1. Nicotine Dependence

Tobacco dependence displays many features of a chronic disease.[18] Nicotine is the key chemical compound that causes and sustains the powerful addicting effects of tobacco products.[19] Research suggests that nicotine may be as addictive as heroin, cocaine or alcohol.[20] Smoking facilitates the delivery of nicotine to the brain. Nicotine in the lungs is rapidly absorbed into the pulmonary venous circulation and then enters the arterial

circulation and moves quickly from the lungs to the brain, where it binds to nicotinic acetylcholine receptors (nAChRs) and triggers the release of dopamine and other neurotransmitters in the mesocorticolimbic brain system. The α4β2 subtype of nAChRs is the principal mediator of nicotine dependence. The binding of nicotine to α4β2 nAChRs stimulates the dopaminergic neurons in the ventral tegmental area of the midbrain that project to the nucleus accumbens and the increased firing of these neurons plays a critical role in drug-induced reward. Extensive investigations over decades have conclusively demonstrated the critical role of the mesocorticolimbic system and its connections in several behavioral and affective responses to drugs of abuse. More recently, other nAChR subtypes, including α3β4- and α6-containing nAChRs, as well as the interplay of the release of the inhibitory neurotransmitter GABA and stimulatory neurotransmitter glutamate in the mesocorticolimbic brain system, have been proposed to also play a role in nicotine dependence. [21]

With repeated exposure to nicotine, neuroadaptation (tolerance) to some of the effects of nicotine develops and the number of binding sites on the nicotinic cholinergic receptors in the brain increases. The satisfaction from smoking cigarettes tends to lessen throughout the day. Desensitization (unresponsiveness of the receptor caused by the prolonged binding of the ligand) is believed to play a role in tolerance and dependence. Desensitized α4β2 nAChRs become responsive again during periods of abstinence, such as nighttime sleep. The binding of nicotine to these receptors during smoking, alleviates craving and withdrawal.[21]

Nicotine induces pleasure and reduces stress and anxiety. Smokers use it to modulate levels of arousal and to control mood. Smoking improves concentration, reaction time, and performance of certain tasks. Cessation of smoking causes the emergence of withdrawal symptoms (described below). The basis of nicotine addiction is the interplay between the positive reinforcements, including enhancement of mood, and avoidance of withdrawal symptoms (negative reinforcement). In addition, conditioning, defined as the association between smoking cues and the anticipated effects of nicotine, which results in the urge to use nicotine, also plays a role. The urge to smoke persists by conditioning after the withdrawal symptoms disappear and contributes to relapse.[21]

3.2. Nicotine Withdrawal

According to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.) (DSM-V),[22] the symptoms of nicotine deprivation that appear after abstinence from tobacco include the following:

- irritability, frustration or anger
- anxiety
- difficulty concentrating
- increased appetite
- restlessness
- depressed mood

- insomnia

Abstinence can also be associated with constipation, coughing, dizziness, dreaming/nightmares, nausea, and sore throat. Craving very commonly occurs with abstinence but is not always included as a withdrawal symptom because it often does not increase with abstinence.[23]

Tobacco withdrawal symptoms usually begin within 24 hours of cutting down or stopping tobacco use, peak within first week of abstinence and last for 2-3 weeks on average.

Approximately 50% of smokers who quit or reduce their smoking for 2 days or more will have symptoms that meet the criteria for tobacco withdrawal as defined by DSM V[22]. The most commonly endorsed symptoms (other than craving) are anxiety, irritability and difficulty concentrating and the least commonly endorsed are symptoms of depressed mood and insomnia.[22] It has been suggested that insomnia during abstinence is characterized by increased awakenings or intense dreams.[23]

4. VARENICLINE MECHANISM OF ACTION

Based on the understanding of the neurobiology of nicotine dependence as described above, and considering the magnitude of the public health problem that smoking creates, Pfizer sought to develop a nicotinic receptor partial agonist of α4β2 nAChRs. The nAChRs are pentameric ligand-gated ion channels composed of α- and/or β-subunits that mediate fast synaptic neurotransmission, and the α4β2 subtype had been shown to play a key role in mediating the addictive effects of nicotine. It was hypothesized that partial agonist activity at the α4β2 subtype would be a useful therapeutic approach for smoking cessation. A partial agonist may act as a 'low-efficacy' nicotine during a quit attempt when nicotine is absent, reducing craving and withdrawal without the abuse liability associated with a full agonist like nicotine. On the other hand, in the presence of nicotine during a relapse, a partial agonist may bind to α4β2 nAChR more strongly than nicotine, thereby attenuating the subjective feelings of reward normally obtained from smoking.

A variety of in vitro and in vivo pharmacology studies indicated that varenicline has the potential to achieve those clinical effects. It binds with high affinity to α4β2 nAChRs (inhibition constant [Ki]=0.4 nM) and acts as a partial agonist with 10%-45% agonist efficacy relative to acetylcholine; it increases mesolimbic dopamine release and reduces nicotine self-administration after oral dosing in rats.

Further studies showed that the presence of pharmacologically relevant unbound concentrations of varenicline result in a functional interaction with human α4β2 nAChRs, causing extensive desensitization and low-level activation of α4β2 nAChRs.[24] This pharmacological profile of varenicline is comparable to that of nicotine levels in smokers, suggesting that, functionally, varenicline may substitute for nicotine during abstinence. In addition, in vitro studies showed that varenicline binds more strongly than nicotine to α4β2 nAChRs and can act as a competitive antagonist of nicotine, potentially blocking the rewarding effects of nicotine.

In conclusion, numerous in vitro and in vivo studies have demonstrated that varenicline functions as a partial agonist at α4β2 containing nAChRs, has high selectivity for that receptor subtype in comparison to other nAChRs, increases mesolimbic dopamine release while inhibiting nicotine-induced mesolimbic dopamine release, and reduces nicotine-self administration in rats.

5. VARENICLINE NEUROPSYCHIATRIC SAFETY DATA

5.1. Overview of Neuropsychiatric Safety Data

There are several sources of data that can be considered to evaluate the association between varenicline and NPS events. These include: nonclinical studies, postmarketing reports, randomized, controlled clinical trials, and large observational studies. These different data sources provide varying levels of evidence in the assessment of potential drug effects, as recognized by the Cochrane Group,[25] an organization internationally recognized for the quality and integrity of its data reviews. Table 1 below, shows the sources of varenicline NPS data available, and some of the strengths and limitations of each source. The data sources are presented in order of increasing level of evidence.[25]

Table 1. The Hierarchy of Evidence Provided by Different Data Sources

Data Source	Description	Strengths Include	Limitations Include
Nonclinical studies[26]	Pharmacological profile and behavioral testing in animal models	Allow early screening for safety signals; allow comparison to other compounds using standardized models	Uncertain extrapolation to neuropsychiatric behavior in humans
Postmarketing reports[27]	Collection of case reports through pharmacovigilance systems	Provide data from real world use in broader populations than those studied in clinical trials; have the potential to detect rare safety signals	Often lack medically important information; are subject to reporting biases (including stimulated reporting) and under-reporting; lack a true denominator (number of patients exposed) which limits event rate estimation; are generally not valid for making drug-drug comparisons; information required to perform an optimal scientific causality assessment can differ significantly according to the nature of the adverse event/reaction

Data Source	Description	Strengths Include	Limitations Include
Observational studies (Population-based)[28,29,30]	Population-based studies that collect data from large numbers of subjects with a common group identity, such as members of a health care system, residents of a state or country; may or may not involve a comparator	Provide real world data on use of a drug by actual patients; can provide reliable estimates of a safety signal; can be designed to test hypotheses about a safety signal; can complement findings from randomized trials	Possible confounding by indication (eg, due to differences in risk factors, indications for treatment or severity of illness)
Randomized, Controlled Clinical Trials (RCTs)[25]	Prospective, experimental study design specifically involving random allocation of participants to interventions.	Able to include well-defined populations with the condition of interest; randomization addresses selection bias; blinding of participants, personnel and outcome assessors (double blind RCT design) addresses the performance and detection biases.	If the population studied is defined too narrowly, the ability to generalize the data to real world populations is limited; studies could have insufficient power to detect an effect of the intervention; patients with AEs may drop out resulting in attrition bias.
Meta-analyses of RCTs[25]	Statistical analyses of combined data from multiple RCTs	Provide an increase in power, diversity of trials, confer an improvement in precision, the ability to answer questions not resolved by individual studies, and allows for testing of the robustness of outcomes through sensitivity analyses.	May provide incorrect outcomes, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not addressed.

RCT=randomized, controlled trial.

Table 2 shows the specific varenicline data available from the sources identified in Table 1, separated by time period (in 2009 and current) to illustrate the accumulation of data since the boxed warning. The table provides links to sections where further details are provided.

Table 2. Totality of NPS Data Available in 2009 and Currently

Data Source	NPS data available in 2009	NPS data available in 2014[a]
Nonclinical studies	Binding data for panel of receptors and in vivo behavioral pharmacology studies (Appendix 3.1)	Additional Pfizer and non-Pfizer in vitro studies and in vivo behavioral pharmacology studies (Appendix 3.2)
Postmarketing reports	Increased reporting rate from September 2007 subsequent to a highly publicized case report (Section 5.2)	Transient 2nd peak in reporting between 3rd quarter 2009 and 3rd quarter 2011 which appeared to be driven by US cases reported by attorneys. Reporting rates subsequently declined and stabilized through the end of 2013, at rates observed prior to 2007 (Section 5.3.1)
Population based observational comparative studies	Observational studies not available	4 observational cohort studies (all non-Pfizer) assessing NPS endpoints such as NPS hospitalizations or emergency department visits, fatal or non-fatal self harm (Section 5.3.3). The number of varenicline patients, patient population, and comparator for each study were:

Data Source	NPS data available in 2009	NPS data available in 2014[a]
		• 31,260 / UK general practice patients / vs NRT • 59,790 / Population of Denmark / vs bupropion • 19,933 / US Military Health System / vs NRT • 14,131 / US Veterans Health Administration / vs NRT
Double Blind, Randomized, Controlled Clinical Trials (DB RCTs)[b]	10 DB RCTs in smokers without psychiatric disorders	18 DB RCTs including 2 DB RCTs conducted in smokers with psychiatric disorders (one in patients with major depressive disorder and the other in patients with stable schizophrenia or schizoaffective disorders) that used psychiatric scales (eg, MADRS, HAM-A, BIS-11, PANSS, C-SSRS) (Section 5.3.2)
	Non-Pfizer trials not available	6 Non-Pfizer DB RCTs, of which 2 enrolled smokers with psychiatric disorders and 4 used psychiatric scales (Section 5.3.2.5)
Meta-analyses of DB RCTs	Meta-analysis of NPS AEs in 10 DB RCTs - 3,091 varenicline and 2,005 placebo patients without a psychiatric history[31]	New meta-analyses or combined analyses of: • NPS AEs in 18 DB RCTs – 5,072 varenicline and 3,449 placebo patients (Section 5.3.2.2.3.2, Section 5.3.2.2.3.3) • Suicidal ideation and/or behavior based on C-SSRS in 5 DB RCTs – 1,130 varenicline and 777 placebo patients (Section 5.3.2.2.3.1) • NPS symptoms measured by MNWS in 8 DB RCTs – 2,403 varenicline and 1,434 placebo patients (Section 5.3.2.3.1)
	Non-Pfizer meta-analyses available not available	3 non-Pfizer meta-analyses of: • NPS AEs in 17 DB RCTs – 8,027 patients • Serious NPS in 14 DB RCTs (of which 1 non- Pfizer) – 3,984 varenicline and 2,349 placebo patients • NPS AEs in 10 DB RCTs - 6,375 patients

a. Clinical trial and observational studies as of 25 February 2014, postmarketing data as of 31 December 2014.
b. DB RCTs that included a minimum of 20 varenicline-treated patients reporting NPS safety data in smokers. DB RCTs were Pfizer sponsored unless otherwise specified.

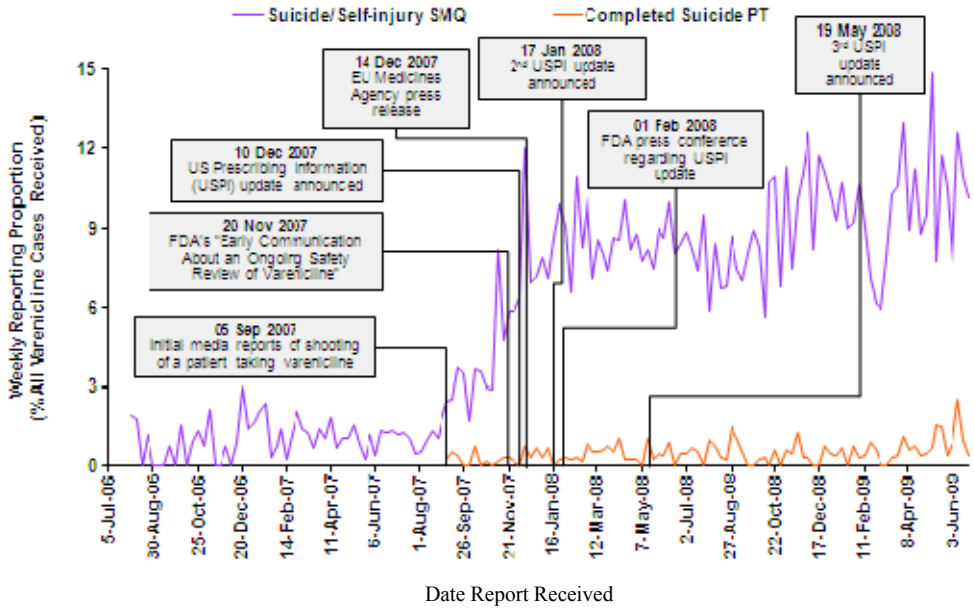
AEs=adverse events; DB=double blind; NPS=neuropsychiatric; RCT=randomized, controlled trial; C-SSRS=Columbia Suicide Severity Rating Scale, HAM-A=Hamilton Anxiety Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; BIS-11=Barrett Impulsiveness Scale; PANSS= Positive and Negative Syndrome Scale; MNWS=Minnesota Nicotine Withdrawal Scale.

5.2. Neuropsychiatric Data Available at the Time of Implementation of the Boxed Warning in 2009

A pharmacological basis for the potential association between varenicline and serious NPS adverse effects was evaluated via the drug's in vitro receptor binding profile and in vivo effects on neurotransmitter release, as well as with preclinical behavioral tests. The results of in vitro studies demonstrated that varenicline has high selectivity for the α4β2 subtype of nAChRs and does not bind to targets that have been implicated in serious NPS adverse effects. The results of the in vivo tests demonstrated that varenicline neither increases nor depletes levels of key cortical neurotransmitters and does not impair behavior in several animal tests that assess effects on mood and cognitive processing. The combined results of nonclinical studies did not provide evidence of an association between varenicline and serious NPS adverse effects.

Postmarketing data from market introduction in 3rd quarter 2006 through 3rd quarter 2007 showed relatively low and stable levels of reporting of serious NPS events. Subsequent to a highly publicized fatal case report in September of 2007, there was a sharp increase in cases reporting multiple categories of serious NPS events. This increase continued as FDA alerts and labeling revisions were announced, as exemplified by the proportion of all spontaneous varenicline case reports that included suicide-related events as shown in Figure 1. Pfizer closely monitored this emerging safety signal for serious NPS events through its pharmacovigilance program and queried the existing clinical database for evidence of an association between varenicline and serious NPS.

Figure 1. Stimulated Postmarketing Reporting of Suicide/Self-Injury Events



A total of 10 randomized, placebo-controlled Pfizer-sponsored varenicline clinical trials had been completed by 2009. These studies provided data from 3,091 subjects treated with varenicline and 2,005 subjects treated with placebo. Subjects with active psychiatric disorders were excluded from the 10 trials based on predetermined inclusion/exclusion criteria. A meta-analysis of the psychiatric AEs reported in the 10 studies was conducted.[31] The analysis of NPS AEs in the 10 studies, showed no apparent increased risk of NPS AEs in any psychiatric High Level Group Term (HLGT), other than those coding to the Sleep disorders and disturbances HLGT, with varenicline treatment compared to placebo (CIs including 1); and when considered together, the RR for psychiatric events other than those related to sleep was 1.02 (95% CI: 0.86, 1.22). Additional details regarding the meta-analysis are provided in Appendix 5.

In summary, in the period leading up to implementation of the boxed warning regarding serious NPS events in the CHANTIX label in July 2009, nonclinical data showed no

pharmacological basis for an association between varenicline and NPS effects, but postmarketing data showed an emerging signal that warranted monitoring and further evaluation. Although the clinical trial data available at the time did not support an increased risk of NPS events compared to placebo, these data were not sufficient to confirm or refute the postmarketing signal due to the small number of such events in the clinical trials.

5.3. Current Neuropsychiatric Data

Since 2009, a substantial amount of additional data regarding NPS events and varenicline treatment have accumulated, including postmarketing reports, recently completed clinical trials, meta-analyses of clinical trial data and published observational studies. These current data, with data cut-off dates of 31 December 2013 for postmarketing data and 25 February 2014 for clinical trial data and literature reports, are described in the sections below.

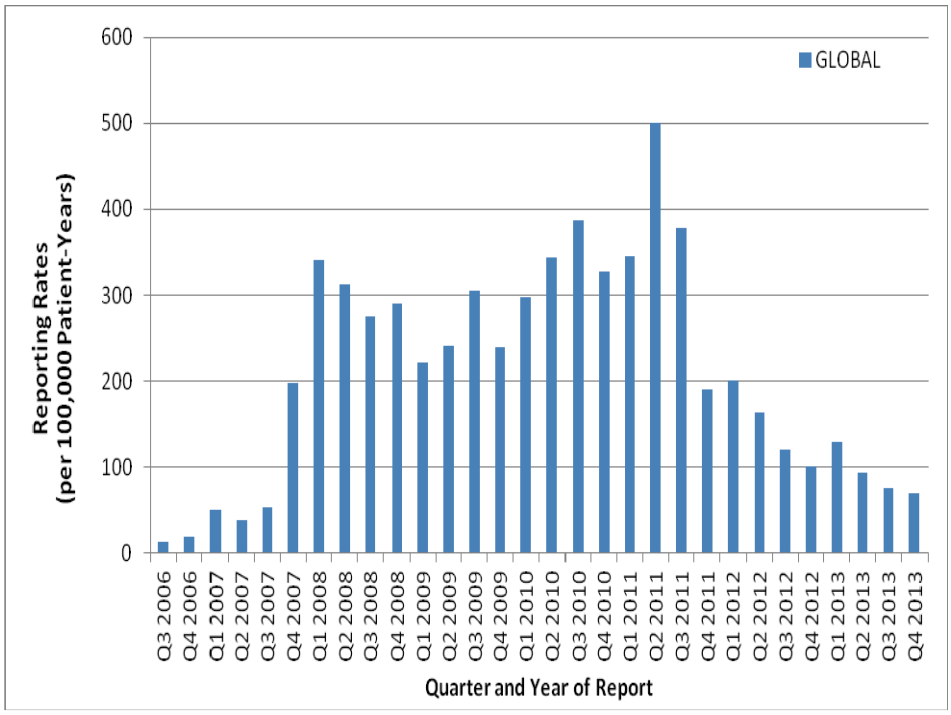
5.3.1. Current Postmarketing Neuropsychiatric Data

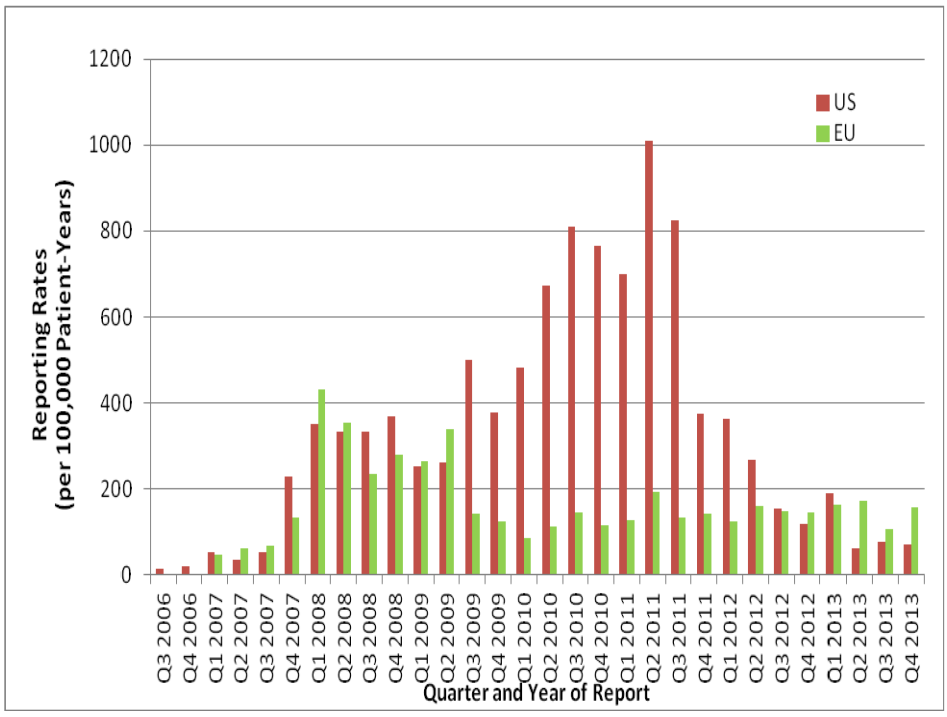
The discussion of postmarketing data presented below focuses on suicide-related events, but other categories of NPS events including depression-related events, hostility/aggression-related events, and psychosis-related events showed similar patterns of reporting. The analysis of each category of NPS event was based on the MedDRA SMQ relevant for that category. Lists of the specific events (Preferred Terms [PTs]) included in the Suicide/Self-injury SMQ can be found in Appendix 2.

5.3.1.1. Suicidal Ideation and/or Behavior

As shown in Figure 1 above, an increase in reporting of suicide-related events was observed following media publicity and regulatory announcements that began in late 2007 and peaked in 1st quarter 2008. As shown in the top graph in Figure 2 below, the global reporting rate (cases per 100,000 patient-years of exposure; for further explanation see Appendix 4.1) of suicidal ideation and/or behavior cases (as based on the Suicide/Self-harm SMQ) declined through 4th quarter 2009 but subsequently increased again in 2011. The bottom graph in the figure shows that this second increase in reporting rates was driven primarily by cases reported in the US. In contrast, in the European Union (EU), reporting rates stabilized after 2nd quarter 2009 and through 4th quarter 2013, with no reporting rate increase as seen in the US.

Figure 2. Global and Regional Quarterly Reporting Rates for Cases with Suicidal Ideation and/or Behavior Events through 4th Quarter 2013

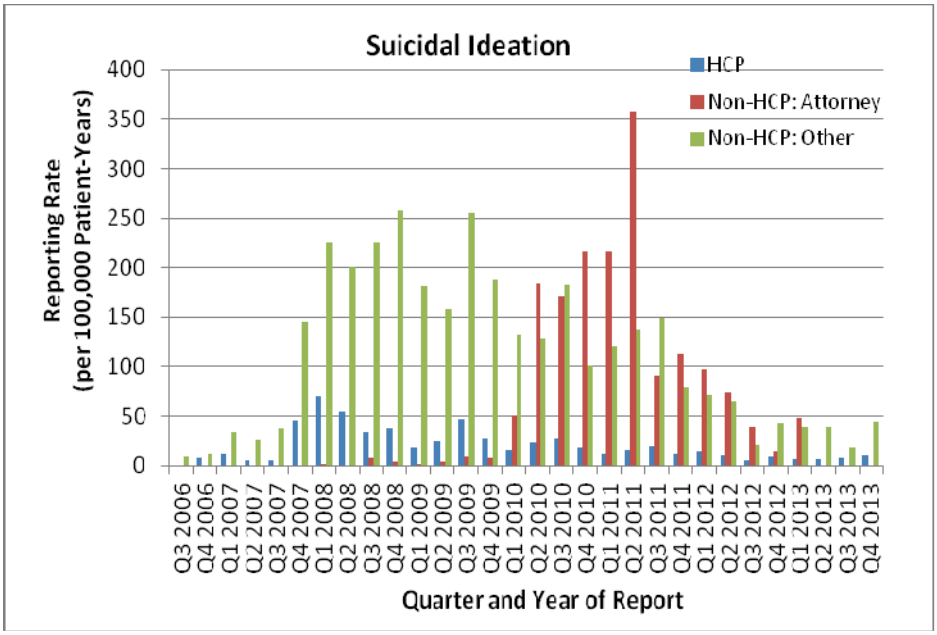


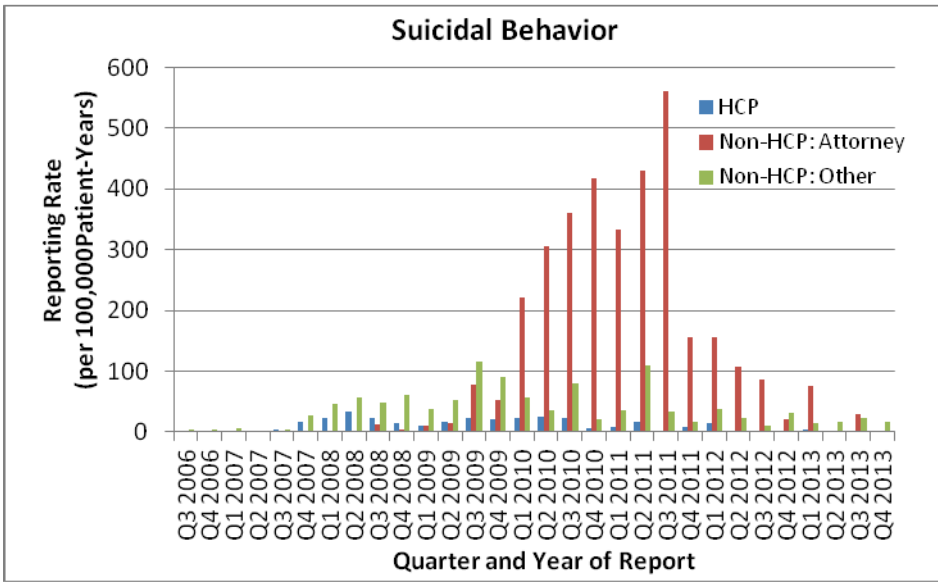


Further evaluation of the US cases related to suicidal ideation (cases with events related to suicidal ideation were defined as cases including the PTs: Depression suicidal, Self-injurious

ideation, Suicidal ideation) and suicidal behavior (cases with events related to suicidal behavior were defined as cases including the PTs: Intentional overdose, Intentional self-injury, Poisoning deliberate, Self-injurious behaviour, Suicidal behaviour, Suicide attempt, Completed suicide) was performed. An analysis based on the source of the report showed that the reporting rates of suicidal ideation and suicidal behavior varied by initial reporter type. As can be seen in Figure 3 for suicidal ideation in the top graph and suicidal behavior in the bottom graph, the reporting rate for cases initially reported by healthcare professionals (eg, physicians, nurses, pharmacists) were relatively low and stable from market introduction through 4th quarter 2013, although small increases were seen coinciding with the media attention in 2007. In contrast, cases initially reported by attorneys started to be received in appreciable numbers after implementation of the boxed warning in July 2009, and then declined after 2nd quarter 2011. Cases initially reported by non-healthcare professionals other than attorneys (eg, patients, friends or family of patients, and others) increased following the media attention in 2007 but showed an overall decline after 3rd quarter 2009.

Figure 3. Quarterly Reporting Rates for US Cases of Suicidal Ideation and Suicidal Behavior by Reporter Type





Suicidal Ideation includes the Preferred Terms: Depression suicidal, Self-injurious ideation, Suicidal ideation. Suicidal Behavior includes the Preferred Terms: Intentional overdose, Intentional self-injury, Poisoning deliberate, Self-injurious behaviour, Suicidal behaviour, Suicide attempt, Completed suicide.

One of the primary limitations of postmarketing reports is that the cases often lack key information necessary for a meaningful clinical interpretation, such as event onset and therapy start/stop dates, clinical outcome (eg, resolved, not resolved, fatal), and information pertinent to confounding factors including medical history and concomitant medications. Additional limitations of postmarketing data are described in Appendix 4.

5.3.2. Current Clinical Trial Neuropsychiatric Data

As noted above, since 2009 and before 25 February 2014, an additional 8 double-blind, randomized, placebo-controlled Pfizer-sponsored varenicline smoking cessation trials have completed, for a total of 18 studies. These 8 studies are summarized in Table 3. Among the 8 are 2 studies specifically designed to include patients with psychiatric co-morbidities. These 2 studies are described in detail in the Section 5.3.2.1 below. In addition, 2 new NPS meta-analyses have been conducted that include data from Pfizer-sponsored placebo-controlled studies and are described in detail in Section 5.3.2.2. The first meta-analysis looked at the Columbia Suicide Severity Rating Scale (C-SSRS), which was administered in 5 recent studies of the 18 total studies (the 5-study cohort); the second looked at a broad range of NPS events and included data from all 18 studies (the 18-study cohort). There have also been literature reports of 6 individual randomized, controlled studies of varenicline versus (vs) placebo or active comparator and 3 independent meta-analyses that were not conducted by Pfizer. These literature reports are summarized in Section 5.3.2.5.

Table 3. Randomized, Placebo-Controlled Varenicline Studies Completed Since 2009 and through 25 February 2014

Study Objective/Population Study Number	Duration	Treatment Groups	Psychiatric Scales Used	Number. of Subjects[a]
COPD **A3051054**	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo		248 251 Total: 499
Schizophrenia/ Schizoaffective disorder **A3051072**	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	C-SSRS, PANSS, BIS-11	84 43 Total: 127
Multinational sites in Africa, Mid-East, S. America **A3051080**	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo		390 198 Total: 588
Flexible quit date **A3051095**	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	C-SSRS, PHQ9	486 165 Total: 651
Smokeless tobacco **A3051104**	12 weeks treatment, plus nontreatment follow-up to Week 26	Varenicline, 1 mg BID: Placebo		213 218 Total: 431
Enforced abstinence **A3051115**	12 weeks treatment, plus 30 day nontreatment follow-up	Varenicline, 1 mg BID: Placebo	C-SSRS, HAM-A. MADRS, OAS-M, POMS	55 55 Total: 110
Depression **A3051122**	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	C-SSRS, MADRS HAM-A BIS-11	256 269 Total: 525
Re-treatment **A3051139**	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	C-SSRS	249 245 Total: 494

BID=twice a day; COPD=Chronic obstructive pulmonary disease; C-SSRS=Columbia Suicide Severity Rating Scale, HAM-A=Hamilton Anxiety Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; POMS=Profile of Mood States; PHQ9= Patient Health Questionnaire; PANSS= Positive and Negative Syndrome Scale; OAS-M= Overt Aggression Scale-modified; BIS-11= Barratt Impulsiveness Scale.

a. Number of Subjects = subjects randomized and treated by treatment group and in total; All studies enrolled smokers with the exception of A3051104 which enrolled smokeless tobacco users.

5.3.2.1. Studies in Subjects with Psychiatric Co-morbidities

Two of the 8 studies completed since July 2009 were designed to include populations of smokers with a psychiatric history, specifically MDD (Depression Study) and schizophrenia/schizoaffective disorder (Schizophrenia Study). In addition to monitoring spontaneously reported and observed AEs, both studies used validated psychometric scales to monitor psychiatric status, as described below.

5.3.2.1.1. Depression Study (A3051122)

The Depression Study included a total of 525 subjects, 256 randomized to varenicline and 269 randomized to placebo. The key inclusion criterion for this study was: current or past diagnosis of MDD without psychotic features, either single or recurrent, using DSM-IV based on clinical assessment and confirmed by the Structured Clinical Interview for DSM Disorders (SCID) and at least 1 of the following: on stable antidepressant treatment for MDD (stable for at least 2 months); major depressive episode, using DSM-IV, in the past 2 years successfully treated. Subjects were treated for 12 weeks and then followed up in the non-treatment phase through Week 52. In addition to the standard collection of AEs (volunteered), NPS AEs were solicited through a semi-structured interview. The interview is not a validated symptom severity or diagnostic instrument, but served to enhance capture of AEs of interest. A battery of psychiatric rating scales was also administered. These included the Montgomery Asberg Depression Rating Scale (MADRS), the Hamilton Anxiety Scale (HAM-A), the 11-item Barrett Impulsiveness Scale (BIS-11), and the C-SSRS.

Most subjects (varenicline, 70.7%; placebo, 73.2%) were receiving antidepressant medications at study entry, with selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors the predominant types (varenicline, 61.3%; placebo, 67.7%).

Mean total scores at baseline were 7.8 for MADRS and 6.3 for HAM-A; both are in the remitted or normal range of scores. Approximately 26% of subjects had a baseline MADRS score greater than 11, the midpoint between remitted and mildly depressed scores.

Varenicline-treated subjects had higher continuous abstinence rates vs placebo at Weeks 9 to 12 (35.9% vs. 15.6%; odds ratio [OR], 3.35 [95% CI: 2.16 to 5.21]; $p < 0.0001$), and Weeks 9 to 52 (20.3% vs. 10.4%; OR, 2.36 [CI: 1.40 to 3.98]; $p = 0.0011$).

Table 4 shows the most common AEs reported (volunteered and solicited) in the Psychiatric disorders SOC. Included in the table are those HLGTs in the Psychiatric disorders SOC reported by ≥2% of subjects in either treatment group and all PTs within those HLGTs.

Table 4. Incidence of Treatment-Emergent Adverse Events (Volunteered and Solicited) in the Psychiatric Disorders SOC Reported in ≥2% of Subjects in Either Treatment Group at the HLGT Level, Depression Study

MedDRA SOC High Level Group Term Preferred Term	Varenicline (N = 256) Number of Subjects (%)	Placebo (N = 269)
PSYCHIATRIC DISORDERS SOC	103 (40.2)	93 (34.6)
Anxiety disorders and symptoms	**39 (15.2)**	**41 (15.2)**
Agitation	17 (6.6)	11 (4.1)
Anxiety	18 (7.0)	25 (9.3)
Nervousness	2 (0.8)	1 (0.4)
Panic attack	2 (0.8)	1 (0.4)
Stress	0	3 (1.1)
Tension	9 (3.5)	8 (3.0)
Changes in physical activity	**5 (2.0)**	**5 (1.9)**
Restlessness	5 (2.0)	5 (1.9)
Depressed mood disorders and disturbances	**28 (10.9)**	**25 (9.3)**
Anhedonia	1 (0.4)	0
Depressed mood	7 (2.7)	10 (3.7)
Depression	17 (6.6)	13 (4.8)
Depression suicidal	1 (0.4)	1 (0.4)
Depressive symptom	2 (0.8)	1 (0.4)
Major depression	1 (0.4)	0
Negative thoughts	1 (0.4)	0
Mood disorders and disturbances NEC	**8 (3.1)**	**7 (2.6)**
Affect lability	2 (0.8)	2 (0.7)
Anger	1 (0.4)	0
Apathy	3 (1.2)	2 (0.7)
Elevated mood	1 (0.4)	1 (0.4)
Mood altered	2 (0.8)	2 (0.7)
Personality disorders and disturbances in behavior	**8 (3.1)**	**2 (0.7)**
Aggression	2 (0.8)	1 (0.4)
Hostility	5 (2.0)	1 (0.4)
Social avoidant behavior	1 (0.4)	0
Sleep disorders and disturbances	**63 (24.6)**	**47 (17.5)**
Abnormal dreams	29 (11.3)	22 (8.2)
Dyssomnia	0	1 (0.4)
Hypnagogic hallucination	0	1 (0.4)
Initial insomnia	1 (0.4)	4 (1.5)
Insomnia	28 (10.9)	13 (4.8)
Middle insomnia	3 (1.2)	3 (1.1)
Nightmare	4 (1.6)	3 (1.1)
Sleep disorder	7 (2.7)	4 (1.5)
Sleep talking	1 (0.4)	0
Terminal insomnia	1 (0.4)	0

Subjects were counted only once per row.
Includes data up to 30 days after last dose of study drug. Includes all HLGTs in the Psychiatric disorders SOC reported by ≥2% of subjects in either treatment group and all PTs within those HLGTs.
HLGT=High Level Group Term; N=total number of subjects; NEC=not elsewhere classified; PT=Preferred Term; SOC=System Organ Class.
MedDRA v16.0.

Subjects in both treatment groups most frequently reported psychiatric AEs within the Sleep disorders and disturbances HLGT; the proportion of varenicline subjects was higher than placebo subjects.

Subjects also frequently reported events within the Anxiety disorders and symptoms HLGT and the Depressed mood disorders and disturbances HLGT; the proportion of subjects was the same or similar in both treatment groups.

A total of 6 subjects experienced serious AEs (SAEs) coding to PTs in the Psychiatric disorders SOC: 2 varenicline subjects (Psychotic disorder in 1 subject and Depression + Suicidal ideation in the other) and 4 placebo subjects (Intentional self-injury, Depression suicidal + Agitation, Agitation, and Depression; 1 subject each). The Intentional self-injury event in the placebo subject was considered treatment related by the Investigator. That event, as well as the Depression + Suicidal ideation events in the single varenicline subject resulted in permanent discontinuation of study drug.

Psychiatric events were the most frequent category of AEs leading to permanent discontinuation of study drug. Including the 2 subjects with SAEs noted above, 10 of 16 varenicline subjects and 16 of 21 placebo subjects who permanently discontinued study drug due to an AE did so due to a psychiatric AE. Most of these events in both treatment groups were considered treatment related by the Investigator.

AEs in the Suicidal and self-injurious behavior HLGT were only reported in placebo subjects (0 varenicline, 5 (1.9%) placebo). Of the 5 placebo subjects, 4 reported ideation events (3 Suicidal ideation, 1 Self-injurious ideation) and 1 reported Intentional self-injury. Additional information about suicidal ideation and behavior was provided by the C-SSRS, which is summarized in Table 5.

Table 5. Summary of the Columbia-Suicide Severity Rating Scale Reponses During Study, Depression Study

Suicidal Ideation and/or Behavior	Varenicline	Placebo
Lifetime		
Subjects assessed, N	256	269
Suicidal behavior, n (%)	23 (9.0)	28 (10.4)
Suicidal ideation, n (%)	86 (33.6)	87 (32.3)
Baseline		
Subjects assessed, N	256	269
Suicidal behavior, n (%)	0	0
Suicidal ideation, n (%)	6 (2.3)	1 (0.4)
Treatment-emergent phase		
Subjects assessed, N	251	268
Suicidal behavior, n (%)	0	1 (0.4)[a]
Suicidal ideation, n (%)	15 (6.0)	19 (7.1)
Follow-up phase		
Subjects assessed, N	209	207
Suicidal behavior, n (%)	1 (0.5)[b]	0
Suicidal ideation, n (%)	12 (5.7)	12 (5.8)

The percentages were based on the number of subjects with an assessment for any given period.
N=total number of subjects; n=number of subjects in subset.

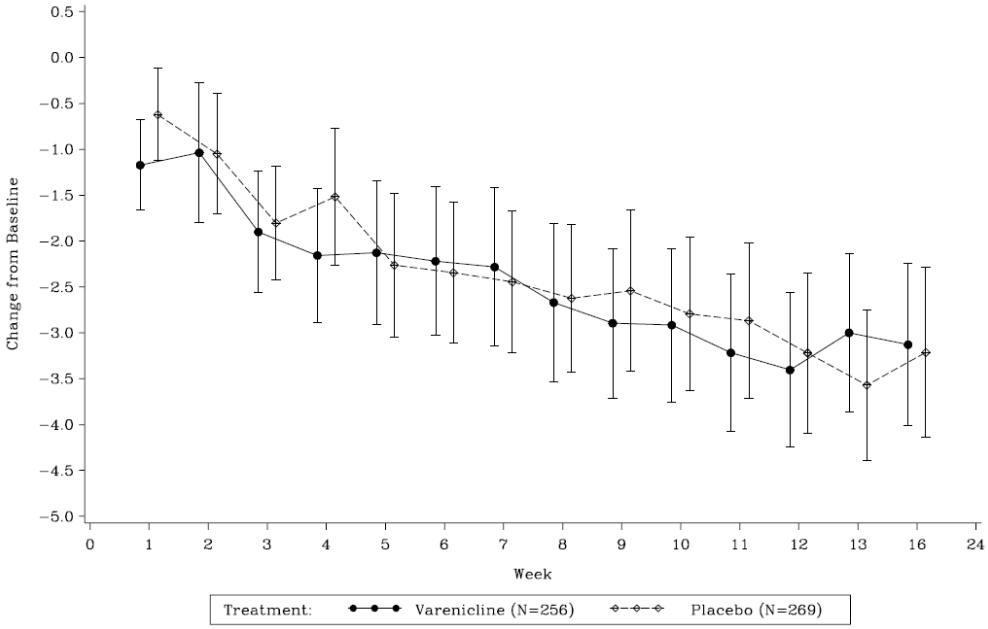
a. 1 subject slit his wrists but denied any intent to kill himself. This event was considered an SAE and was ultimately coded to Intentional self-injury in the clinical and safety databases.

b. 1 subject died due to an overdose of illicit drugs. The SAE was ultimately coded as Overdose in the clinical and safety databases. The case was conservatively counted by the Sponsor as a possible suicide in this table.

A higher proportion of varenicline than placebo subjects reported suicidal ideation at baseline (2.3% vs 0.4%, respectively), whereas the proportion reporting suicidal ideation was modestly lower in varenicline than placebo subjects (6.0% vs 7.1%, respectively) during the treatment period, and similar in the follow-up phase (5.7% vs 5.8%, respectively). Suicidal behaviors were reported by 2 subjects. There was 1 event of intentional self-injury/possible suicide attempt during treatment (Study Day 73) in a placebo subject with a history of alcohol abuse. A possible suicide could not be ruled out in a varenicline subject who died by an overdose of illicit drugs 76 days after the last dose of study drug.

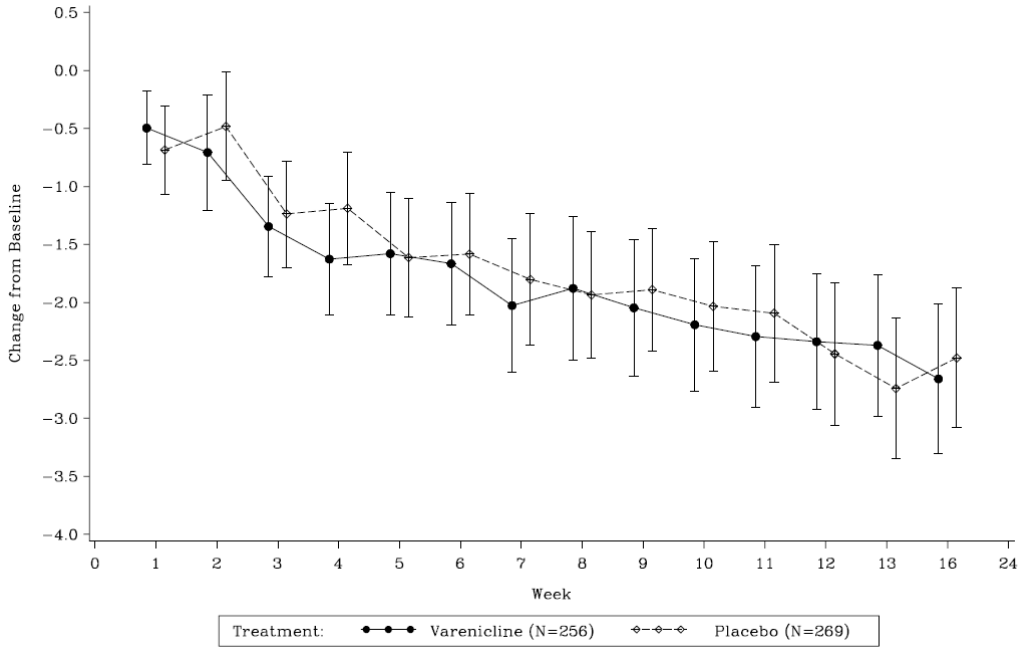
The MADRS, HAM-A and BIS-11 scales were administered at each clinic visit through Week 16. Changes from baseline through Week 16 for MADRS and HAM-A were small and in a clinically favorable direction (numerically lower scores) in both treatment groups. For BIS-11, the mean change from baseline was minimal in both groups (ranging from -0.6 to 0.6). Changes from Baseline for MADRS, HAM-A, and BIS-11 are shown graphically in Figure 4, Figure 5, and Figure 6, respectively.

Figure 4. Plot of Montgomery-Åsberg Depression Rating Scale Mean Change from Baseline (95% CI) by Study Week, Depression Study



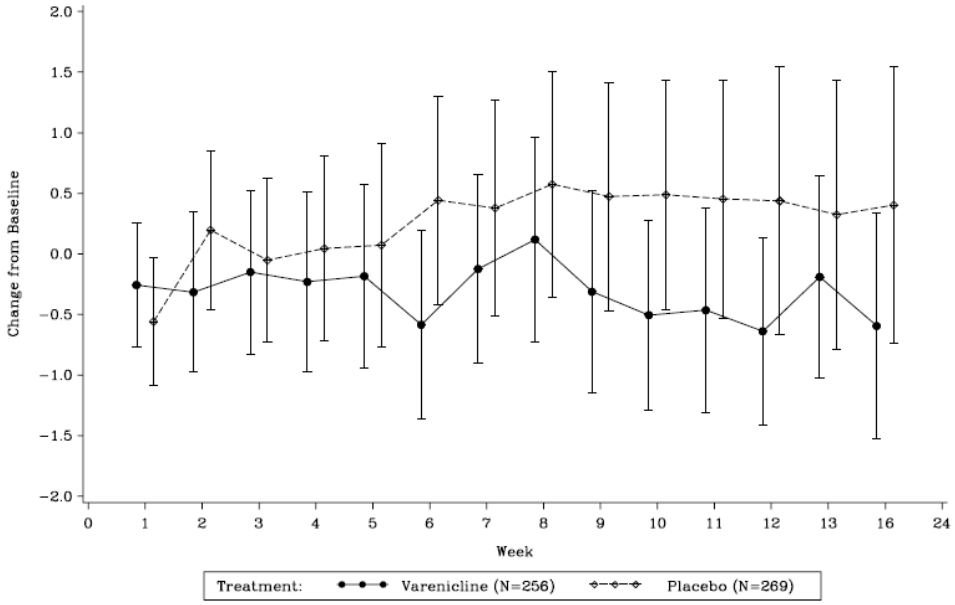
CI=confidence interval; N=total number of subjects (safety analysis set).

Figure 5. Plot of Hamilton Anxiety Rating Scale Mean Change from Baseline (95% CI) by Study Week, Depression Study



CI=confidence interval; N=total number of subjects (safety analysis set).

Figure 6. Plot of Barratt Impulsiveness Scale Total Score Mean Change from Baseline (95% CI) by Study Week, Depression Study



CI=confidence interval; N=total number of subjects (safety analysis set).

5.3.2.1.2. Schizophrenia Study (A3051072)

The Schizophrenia Study included a total of 128 subjects, 85 randomized to varenicline (84 of whom took at least 1 dose of study medication) and 43 randomized to placebo per the 2:1 randomization design. The primary inclusion criterion for this study was a diagnosis (using the SCID at screening) of schizophrenia or schizoaffective disorder using DSM-IV criteria and judged to be stable (without hospitalization or acute exacerbation and functioning in society) on psychiatric treatment for at least 6 months prior to the study. Subjects were treated for 12 weeks and followed up post-treatment through Week 24. In addition to monitoring AEs, psychiatric scales were used including the Positive and Negative Syndrome Scale (PANSS) and the C-SSRS.

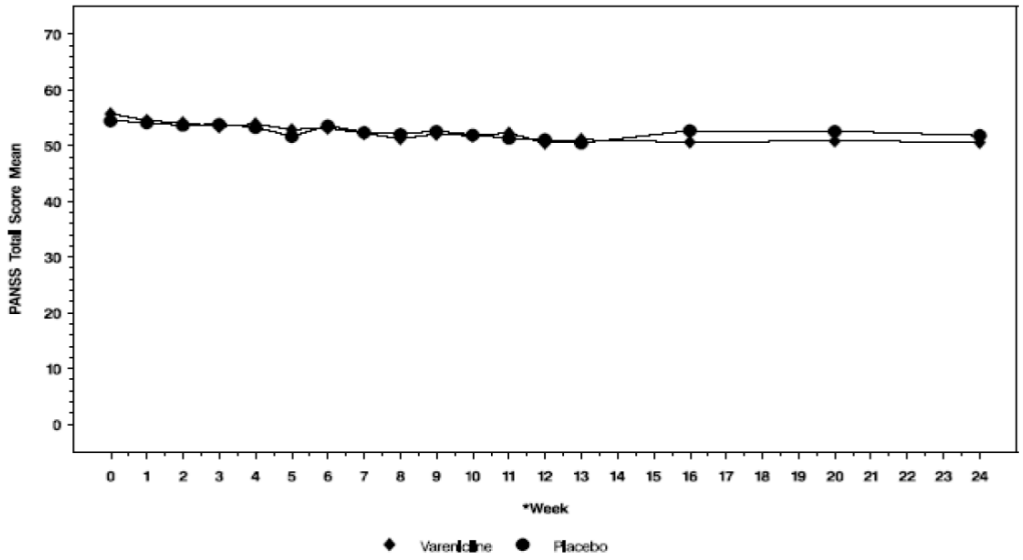
A higher percentage of subjects randomized to varenicline were abstinent from smoking compared to placebo at both Week 12 (19.0% vs 4.7%) and Week 24 (11.9% vs 2.3%), as measured by the 7-day Point Prevalence. The difference reached statistical significance only at Week 12 (p=0.0457).

Among the NPS AEs, events that occurred at a rate ≥2% (ie, in more than 1 subjects in either treatment group) and more frequently in varenicline than in placebo subjects included: Depressed mood (2.4% vs 2.3%), Hallucination auditory (4.8% vs 2.3%), Insomnia (9.5% vs 4.7%), and Paranoia (2.4% vs 0%).

The PANSS was administered to monitor psychotic symptoms during the study. Mean total scores at baseline were comparable between treatment groups (55.9 for varenicline and 54.5 for placebo) and reflected an average rating for all questions corresponding to mild symptoms. Total positive and negative scores remained stable with very small decreases

(lower scores reflect improvement in symptoms) from baseline to Week 12 (end of treatment) and Week 24 (end of follow-up period) observed in both groups, indicating no worsening of psychotic symptoms. PANSS Total score is shown in Figure 7.

Figure 7. Mean of PANSS Total Score by Study Visit; Schizophrenia Study



Suicidal ideation and behavior were monitored using the C-SSRS, as well as AE data during the study. Table 6 summarizes "yes" responses to C-SSRS questions in all study phases.

Table 6. Summary of "Yes" Answers on the Columbia Suicide Severity Rating; Schizophrenia Study

Suicidal Behavior and/or Ideation	Varenicline	Placebo
Lifetime		
Subjects assessed, N [a]	84	43
Suicidal ideation or behavior, n (%)	52 (61.9)	22 (51.2)
Baseline		
Subjects assessed, N	84	42
Suicidal ideation or behavior, n (%)	0 (0)	1 (2.4)
Treatment phase		
Subjects assessed, N	82	43
Suicidal ideation or behavior, n (%)	9 (11.0)	4 (9.3)
Post-treatment follow-up phase		
Subjects assessed, N	70	39
Suicidal ideation or behavior, n (%)	8[b] (11.4)	2[c] (5.1)

C-SSRS = Columbia Suicide Severity Rating Scale
a. Table includes subjects who took at least 1 dose of study medication.
b. Includes 6 subjects with "yes" answers during the post-treatment phase only, and 2 subjects who had "yes" answers during both the treatment and post-treatment phases.
c. Subjects had "yes" answers during both the treatment and the post-treatment phases.

Over half of the subjects had a lifetime history of suicidal ideation and/or behavior on the C-SSRS (62% on varenicline vs 51% on placebo), but at baseline, no subjects in the varenicline group reported suicidal ideation and/or behavior vs 1 in the placebo group (2%). Suicidal ideation and/or behavior were reported in 11% of the varenicline-treated and 9% of the placebo-treated patients during the treatment phase. During the post-treatment phase (through Week 24), suicidal ideation and/or behavior were reported in 11% of patients in the varenicline group and 5% of patients in the placebo group. Many of the patients reporting suicidal behavior and ideation in the follow-up phase had not reported such experiences in the treatment phase. However, no new suicidal ideation or behavior emerged in either treatment group shortly (within 1 week) after treatment discontinuation. There were no completed suicides. There was 1 suicide attempt in a varenicline-treated patient whose lifetime history included several similar attempts.

5.3.2.2. 5-Study and 18-Study Meta-Analyses

A total of 18 placebo-controlled studies completed as of the 25 February 2014 cut-off date for clinical data in this Briefing Document. Pfizer conducted a meta-analysis of pooled data from all 18 studies. The 18 studies are described in Table 3 and Table 18 and included 5,072 varenicline and 3,449 placebo subjects. Five of these 18 studies utilized the C-SSRS, and a meta-analysis of pooled C-SSRS data from those studies was also conducted. These 5 studies (A3051072, A3051095, A3051115, A3051122, and A3051139) included 1,130 varenicline and 777 placebo subjects.

5.3.2.2.1. Outcomes Assessed

Suicidal ideation and behavior were analyzed based on responses to the C-SSRS, using the 5-study cohort, and based on AEs coded to PTs within the Suicide/Self-Injury SMQ and the Suicidal self-injurious behaviors NEC HLGT using the 18-study cohort. Aggressive behavior and violence were analyzed based on the Hostility/Aggression SMQ (18-study cohort). For overall psychiatric events, the HLGTs within the Psychiatric Disorders SOC were analyzed as well as a composite endpoint including all combined psychiatric AEs from the SOC excluding the Sleep Disorders and Disturbances HLGT (18-study cohort). See Appendix 2 for a list of the PTs included in each of the SMQs analyzed.

C-SSRS endpoints were summarized as the number of subjects with "yes" answers for suicidal ideation (any type), suicidal behavior (any type), ideation and/or behavior and for self-injurious behavior with no suicidal intent, based upon the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories[32]. Descriptive data for subtypes of ideation and behavior are provided.

AEs were summarized by SOC and HLGT or by SMQs. All subjects who took at least 1 dose of study drug were included. As noted in Section 5.3.2.1, in Study A3051122 (Depression study), in addition to the collection of volunteered AEs, NPS AEs were solicited through a a semi-structured interview.

The majority of the 18 studies excluded smokers with psychiatric disorders such as current or past panic disorder, bipolar disorder or psychosis, depression requiring treatment within the

last year, recent drug or alcohol abuse. The 2 exceptions were the Depression Study and the Schizophrenia Study, which were described above in Section 5.3.2.1.

5.3.2.2.2. Statistical Methods

No formal hypothesis testing was performed and no adjustments for multiplicity were imposed. The analysis of suicidal ideation and/or behavior reported on the C-SSRS during treatment was considered the primary analysis. All other suicide-related analyses as well as analyses of aggressive behavior/violence events were considered secondary. The analysis of overall psychiatric AEs was considered tertiary.

Meta-analyses were performed for endpoints with 5 or more events overall (both treatment groups combined). Endpoints with fewer than 5 events overall were summarized descriptively (number [%] subjects by treatment group). Analyses were conducted for treatment-emergent events (TEAE), defined as events that began on or after the first day of study treatment and within 30 days after the last dose of study drug (referred to as the 'during treatment' period). In addition, for the C-SSRS, sensitivity analyses over the entire study period (during treatment + follow-up period of up to 40 weeks after the last dose; referred to as the 'during study' period) were also conducted using the same methods as in the 'during treatment' analyses.

Suicidal ideation and/or behavior outcomes (derived from the C-SSRS) were analyzed using Poisson regression models with SAS PROC GENMOD. The models included study as a covariate and treatment group as the explanatory variable. Risk ratios (RRs), RDs and two-sided 95% CIs were calculated by study and overall for the comparisons between varenicline and placebo. Some models for endpoints derived from the C-SSRS also included the presence or absence of pre-dose history of suicidal ideation and/or behavior as an additional covariate.

All outcomes based on TEAEs (Suicide/Self-injury SMQ, Hostility/Aggression SMQ, and HLGTs in the Psychiatric Disorders SOC) were analyzed using Cochran-Mantel-Haenszel (CMH) statistics stratified by study. RRs, RDs and two-sided 95% confidence intervals were calculated by study and overall for the comparisons between varenicline and placebo.

In addition, heterogeneity across studies was assessed for all the meta-analyses performed. Forest plots were used to graphically display the results of all the meta-analyses. Combined study results are shown as a diamond centered at the point estimate with lateral points equal to the lower and upper 95% confidence limits. In the forest plots based on the CMH method, the symbols for the point estimates for each study are sized in proportion to their CMH weight.

In both the Poisson regression models and the CMH statistics meta-analyses, studies with zero events in both treatment groups did not contribute to the overall results, except for the CMH RD analyses, which included them. Since estimation for multiple endpoints was not adjusted for multiplicity, a false-positive result could have occurred by chance.

The number and percent of subjects with 'yes' answers to each C-CASA category and sub-category on the C-SSRS were tabulated by study and for the 5-study cohort for the 3 study periods of: pre-dosing (including all responses collected up to but not including date of first dose [lifetime+baseline]), during treatment (as defined above) and during study (as defined above). Additionally, during treatment C-SSRS responses were summarized by subjects with and without a pre-dose history of suicidal ideation and/or behavior.

Analyses were performed using SAS software version 9.2.

5.3.2.2.3. Results of the 5-Study and 18-Study Meta-Analyses

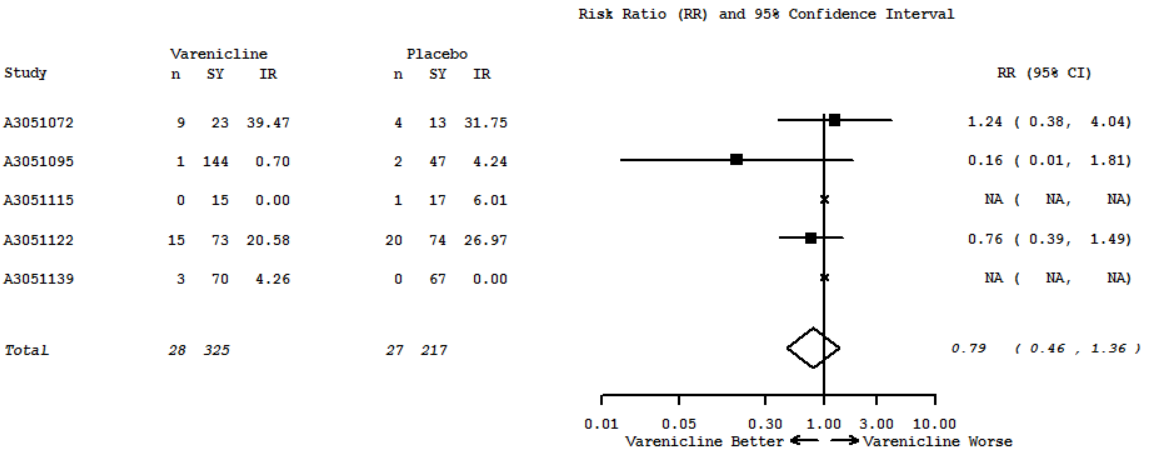
5.3.2.2.3.1. Suicidal Ideation and Behavior

5.3.2.2.3.1.1. C-SSRS – 5-Study Cohort

The 5-study cohort included 1,130 varenicline-treated subjects and 777 placebo-treated subjects; all subjects with C-SSRS evaluations pre and/or post baseline were included in the analysis. There were 28 varenicline subjects and 27 placebo subjects who reported suicidal ideation and/or behavior on the C-SSRS in the during the treatment period. Twenty-four of the 28 varenicline subjects and 24 of the 27 placebo subjects were from the 2 studies in subjects with psychiatric co-morbidities (the Depression Study and the Schizophrenia Study).

The estimate of the RR for varenicline vs placebo, during treatment, per 100 subject-years was 0.79 (95% CI: 0.46, 1.36) and is shown in Figure 8. The RD, during treatment, per 100 subject-years was -1.14 (95% CI: -4.64, 2.35) and is shown in Figure 9.

Figure 8. Subjects with Suicidal Ideation and/or Behavior Reported on C-SSRS During Treatment: RR (95% CI) Varenicline vs Placebo, per 100 Subject-Years; 5-Study Cohort



During Treatment Includes Data Up to 30 Days After the Last Dose of Study Drug.
Heterogeneity: CHISQ = 2.39, df = 2, P = 0.3025.
IR = Incidence Rate per 100 Subject-Years (SY), NA = Not applicable (zero events in at least one group).
Poisson model includes terms for protocol, treatment and previous history of suicidal ideation or behavior.
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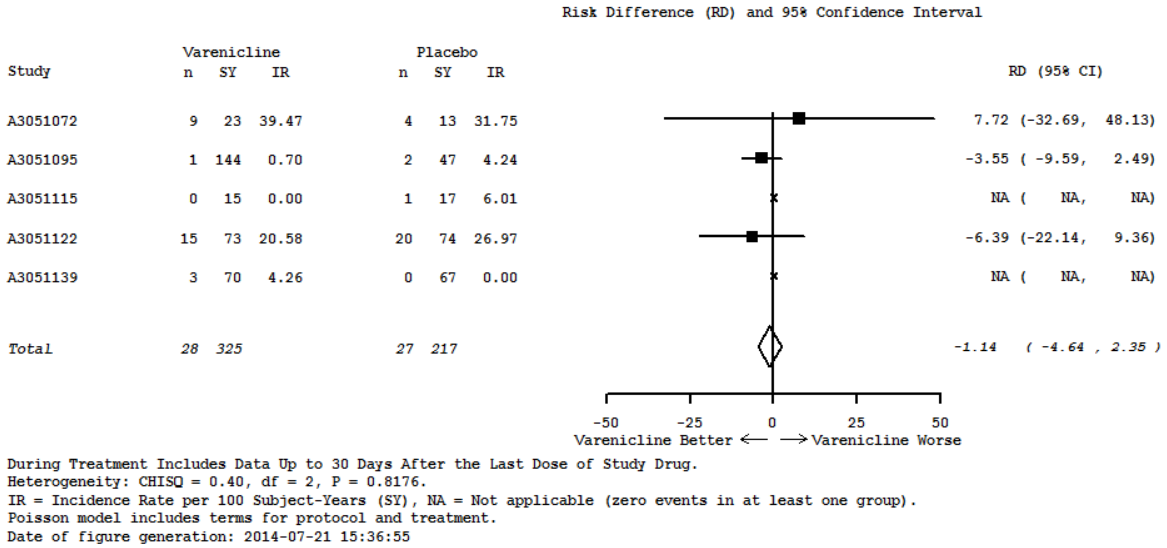
Figure 9. Subjects with Suicidal Ideation and/or Behavior Reported on C-SSRS During Treatment: RD (95% CI) Varenicline versus Placebo, per 100 Subject-Years; 5-Study Cohort



An overview of the RRs and RDs (95% CI) for suicidal ideation and behavior reported on the C-SSRS for varenicline vs placebo by the 2 reporting periods "during treatment" (treatment + 30 days) and "during study" (during treatment + follow-up period of up to 40 weeks after the last dose) and adjustment for exposure is shown in Table 7 below.

Table 7. Subjects with Suicidal Ideation and/or Behavior Reported on C-SSRS: RRs and RDs (95% CI) Varenicline vs Placebo by Reporting Period; 5-Study Cohort

Outcome	RR (95% CI)	RD (95% CI)
Suicidal Ideation and/or Behavior		
During treatment, per 100 subject-years	0.79 (0.46, 1.36)	-1.14 (-4.64, 2.35)
During treatment	0.81 (0.47, 1.39)	-0.28 (-1.29, 0.72)
During study, per 100 subject-years[a]	1.11 (0.71, 1.76)	1.33 (-1.72, 4.39)
During study[a]	1.15 (0.72, 1.82)	0.17 (-1.03, 1.37)
Suicidal Ideation		
During treatment, per 100 subject-years	0.82 (0.48, 1.42)	-1.08 (-4.55, 2.39)
During treatment	0.84 (0.49, 1.45)	-0.27 (-1.26, 0.73)
During study, per 100 subject-years	1.12 (0.70, 1.78)	1.33 (-1.70, 4.37)
During study	1.15 (0.72, 1.83)	0.17 (-1.03, 1.37)

During treatment = first dose to 30 days after the last dose of study drug
During study = first dose to the end of the study (treatment+follow-up period of up to 40 weeks after the last dose)
a. 1 subject died due to an overdose of illicit drugs in the follow-up phase, which was considered by the sponsor as a possible suicide.

As shown in Table 7, the estimates for the RRs range from 0.79 to 1.15 and all 95% CIs include 1, while the estimates for RDs range from -1.14 to 1.33 and all 95% CIs include 0, such that both assessments indicate no significant difference in suicidal ideation and/or behavior for varenicline vs placebo.

There were 3 subjects in total for whom Suicidal Behavior was reported on the C-SSRS (1 varenicline during treatment, 1 varenicline post-treatment (subject who had an illicit drug overdose, considered a possible suicide although intent was not clear from the information provided) and 1 placebo during treatment) and 4 subjects for whom Non-Suicidal Self-Injurious Behavior was reported (1 varenicline post-treatment, 1 placebo during treatment and 2 placebo post-treatment). As there were too few subjects reporting events on the C-SSRS for each of these categories, a formal meta-analysis was not conducted for Suicidal Behavior and Non-Suicidal Self-Injurious Behavior; however, these events are included in the analysis of combined category of Suicidal Ideation and/or Behavior.

Table 8 below presents the total number of varenicline and placebo subjects reporting each type of ideation or behavior (C-CASA category and subcategory) in the 5-study cohort by study period (pre-dosing, during treatment, during study).

Table 8. Subjects Reporting each Type of Suicidal Ideation and Behavior (C-CASA categories) on C-SSRS by Treatment and Study Period; 5-Study Cohort

	Varenicline N=1,130 n (%)	Placebo N=777 n (%)
Pre-dosing (Lifetime and Baseline)		
Number Assessed	1130	777
Suicidal Behavior and/or Ideation	173 (15.3)	120 (15.4)
Suicidal Behavior	64 (5.7)	44 (5.7)
Completed Suicide <1>	0 (0)	0 (0)
Suicidal Attempt <2>	58 (5.1)	35 (4.5)
Preparatory Acts Toward Imminent Suicidal Behavior <3>	40 (3.5)	27 (3.5)
Aborted Attempt	19 (1.7)	18 (2.3)
Interrupted Attempt	14 (1.2)	9 (1.2)
Preparatory Acts or Behavior	29 (2.6)	17 (2.2)
Suicidal Ideation <4>	168 (14.9)	118 (15.2)
Wish to Die	157 (13.9)	110 (14.2)
Active Suicidal Thought	96 (8.5)	72 (9.3)
Active Suicidal Thought with Method	70 (6.2)	47 (6)
Active Suicidal Thought with Intent	47 (4.2)	33 (4.2)
Active Suicidal Thought with Plan and Intent	50 (4.4)	31 (4)
Self Injurious Behavior, no Suicidal Intent <7>	21 (1.9)	28 (3.6)
During Treatment (first dose to 30 days after last dose of study drug)		
Number Assessed	1130	777
Suicidal Behavior and/or Ideation	28 (2.5)	27 (3.5)
Suicidal Behavior	1 (0.1)	1 (0.1)
Completed Suicide <1>	0 (0)	0 (0)
Suicidal Attempt <2>	0 (0)	1 (0.1)

Table 8. Subjects Reporting each Type of Suicidal Ideation and Behavior (C-CASA categories) on C-SSRS by Treatment and Study Period; 5-Study Cohort

	Varenicline N=1,130 n (%)	Placebo N=777 n (%)
Preparatory Acts Toward Imminent Suicidal Behavior <3>	1 (0.1)	0 (0)
Aborted Attempt	1 (0.1)	0 (0)
Interrupted Attempt	0 (0)	0 (0)
Preparatory Acts or Behavior	1 (0.1)	0 (0)
Suicidal Ideation <4>	28 (2.5)	26 (3.3)
Wish to Die	25 (2.2)	25 (3.2)
Active Suicidal Thought	12 (1.1)	9 (1.2)
Active Suicidal Thought with Method	7 (0.6)	7 (0.9)
Active Suicidal Thought with Intent	2 (0.2)	3 (0.4)
Active Suicidal Thought with Plan and Intent	1 (0.1)	2 (0.3)
Self Injurious Behavior, no Suicidal Intent <7>	0 (0)	1 (0.1)
During study (treatment+follow-up of 40 weeks after last dose)		
Number Assessed	1130	777
Suicidal Behavior and/or Ideation [a]	46 (4.1)	32 (4.1)
Suicidal Behavior[a]	2 (0.2)	1 (0.1)
Completed suicide [a] <1>	1 (0.1)	0 (0)
Suicidal Attempt <2>	0 (0)	1 (0.1)
Preparatory Acts Toward Imminent Suicidal Behavior <3>	1 (0.1)	0 (0)
Aborted Attempt	1 (0.1)	0 (0)
Interrupted Attempt	0 (0)	0 (0)
Preparatory Acts or Behavior	1 (0.1)	0 (0)
Suicidal Ideation <4>	45 (4)	31 (4)
Wish to Die	38 (3.4)	30 (3.9)
Active Suicidal Thought	22 (1.9)	12 (1.5)
Active Suicidal Thought with Method	10 (0.9)	9 (1.2)
Active Suicidal Thought with Intent	3 (0.3)	4 (0.5)
Active Suicidal Thought with Plan and Intent	1 (0.1)	2 (0.3)
Self Injurious Behavior, no Suicidal Intent <7>	1 (0.1)	3 (0.4)

Subjects are only counted once per row but can be counted in multiple rows
C-CASA category: <#>
a. 1 subject died 76 days after last dose of study treatment. The SAE resulting in death for this patient was Overdose, however the reason for death was noted by the Sponsor as 'Possible Suicide'. The patient is included in this table as a suicide during 'Follow-up' period.

Table 9 shows the types of suicidal ideation and behaviors reported during treatment (first dose to 30 days after last dose of study drug) based on pre-dosing history (Lifetime or Baseline) on the C-SSRS.

Table 9. Subjects Reporting each Type of Suicidal Ideation and Behavior (C-CASA Categories) on C-SSRS During Treatment by Pre-dosing C-SSRS History; 5-Study Cohort

	Varenicline n (%)	Placebo n (%)
Subjects with positive pre-dosing history (Lifetime or Baseline) on C-SSRS	173	120

Table 9. Subjects Reporting each Type of Suicidal Ideation and Behavior (C-CASA Categories) on C-SSRS During Treatment by Pre-dosing C-SSRS History; 5-Study Cohort

	Varenicline n (%)	Placebo n (%)
Suicidal Ideation and Behavior During Treatment		
Suicidal Behavior and/or Ideation	23 (13.3)	17 (14.2)
Suicidal Behavior	1 (0.6)	1 (0.8)
Completed Suicide <1>	0 (0)	0 (0)
Suicidal Attempt <2>	0 (0)	1 (0.8)
Preparatory Acts Toward Imminent Suicidal Behavior <3>	1 (0.6)	0 (0)
Aborted Attempt	1 (0.6)	0 (0)
Interrupted Attempt	0 (0)	0 (0)
Preparatory Acts or Behavior	1 (0.6)	0 (0)
Suicidal Ideation <4>	23 (13.3)	16 (13.3)
Wish to Die	20 (11.6)	16 (13.3)
Active Suicidal Thought	10 (5.8)	6 (5)
Active Suicidal Thought with Method	6 (3.5)	5 (4.2)
Active Suicidal Thought with Intent	2 (1.2)	3 (2.5)
Active Suicidal Thought with Plan and Intent	1 (0.6)	1 (0.8)
Self Injurious Behavior, no Suicidal Intent <7>	0 (0)	0 (0)
Subjects without pre-dosing history on C-SSRS	957	657
Suicidal Ideation and Behavior During Treatment		
Suicidal Behavior and/or Ideation	5 (0.5)	10 (1.5)
Suicidal Behavior	0 (0)	0 (0)
Completed Suicide <1>	0 (0)	0 (0)
Suicidal Attempt <2>	0 (0)	0 (0)
Preparatory Acts Toward Imminent Suicidal Behavior <3>	0 (0)	0 (0)
Aborted Attempt	0 (0)	0 (0)
Interrupted Attempt	0 (0)	0 (0)
Preparatory Acts or Behavior	0 (0)	0 (0)
Suicidal Ideation <4>	5 (0.5)	10 (1.5)
Wish to Die	5 (0.5)	9 (1.4)
Active Suicidal Thought	2 (0.2)	3 (0.5)
Active Suicidal Thought with Method	1 (0.1)	2 (0.3)
Active Suicidal Thought with Intent	0 (0)	0 (0)
Active Suicidal Thought with Plan and Intent	0 (0)	1 (0.2)
Self Injurious Behavior, no Suicidal Intent <7>	0 (0)	1 (0.2)

During treatment = first dose to 30 days after last dose of study drug.
Subjects are counted only once per row but could be counted in multiple rows
C-CASA category: <#>

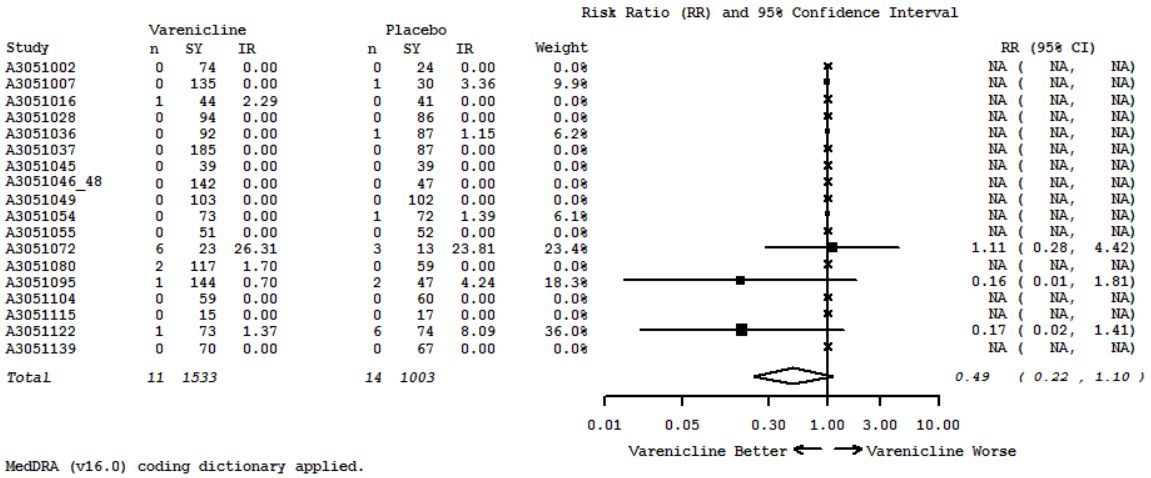
As presented in Table 8 and Table 9, of the 28 varenicline subjects reporting suicidal ideation and/or behavior on the C-SSRS in the during treatment period the majority (23 [82%]) had a

pre-dosing C-SSRS positive history and of the 27 placebo subjects with such reports, the majority (17 [63%]) had a pre-dosing C-SSRS positive history.

5.3.2.2.3.1.2. Suicide/Self-Injury SMQ; 18-Study Cohort

Eleven (11) of 5,072 varenicline-treated subjects and 14 of 3,449 placebo-treated subjects reported TEAEs coding to PTs in the Suicide/Self-injury SMQ in the 18-study cohort. The estimates for RR and RD for varenicline vs placebo, during treatment, per 100 subject-years were 0.49 (95% CI 0.22, 1.10) and -0.74 (95% CI -1.60, 0.13), respectively, and are shown in Figure 10 and Figure 11, respectively.

Figure 10. Risk Ratios (95% CI) of Incidence Rates for Suicide/Self-Injury SMQ During Treatment; 18-Study Cohort



MedDRA (v16.0) coding dictionary applied.
During Treatment Includes Data Up to 30 Days After the Last Dose of Study Drug.
Heterogeneity: Q = 3.09, df = 2, P = 0.2136, I_SQ = 35.2%.
IR = Incidence Rate per 100 Subject-Years (SY), NA = Not applicable (zero events in at least one group).
Mantel-Haenszel Model With Weights = Placebo Events * Varenicline Exposure/Total Exposure.
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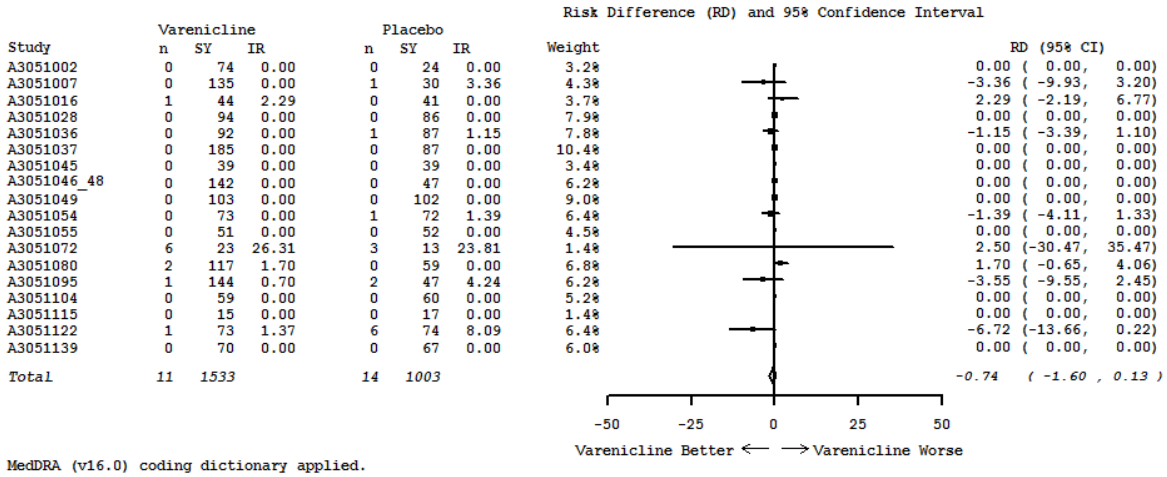
Figure 11. Risk Differences (95% CI) of Incidence Rates for Suicide/ Self-Injury SMQ; 18-Study Cohort



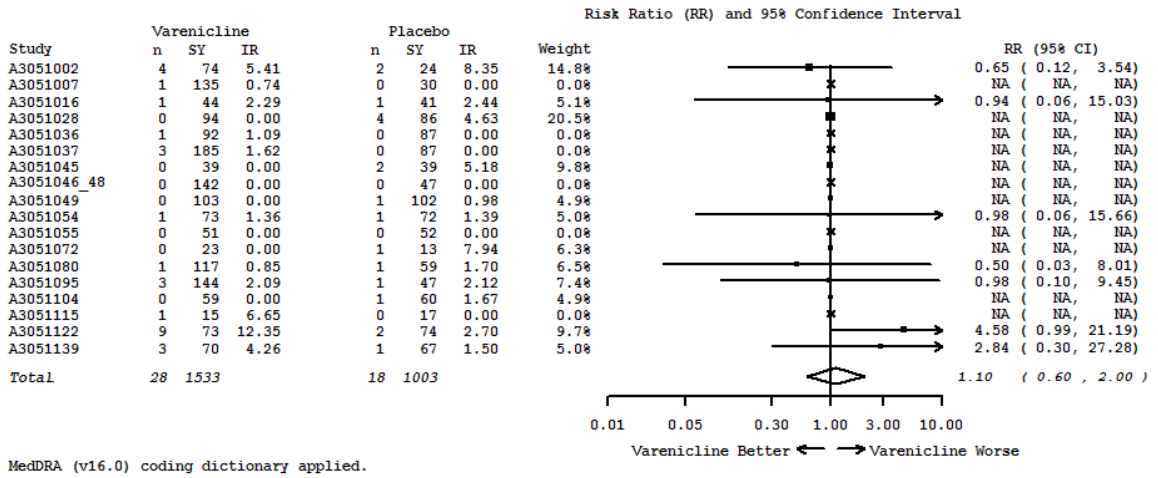
There were 2 varenicline subjects and 2 placebo subjects who reported TEAEs coding to PTs in the suicidal/self-injurious behavior subset of the SMQ.

In summary, the results of the 5-study and the 18-study meta-analyses, which looked at events related to suicidal ideation and/or behavior from the perspective of the C-SSRS and AEs coding to the Suicide/Self-injury SMQ, respectively, were consistent in showing no difference between varenicline and placebo. The RR of suicidal ideation and/or behavior reported on C-SSRS during the treatment period for varenicline vs placebo, per 100 subject-years of exposure in the 5-study cohort was 0.79 (95% CI 0.46, 1.36). The analyses for suicidal ideation separately or by study phase, as well as the analysis of the Suicide/Self-injury SMQ in the 18-study cohort showed comparable results between varenicline and placebo.

5.3.2.2.3.2. Hostility/Aggression SMQ; 18-Study Cohort

Twenty-eight (28) of 5,072 subjects treated with varenicline and 18 of 3,449 subjects treated with placebo reported TEAEs coding to PTs in the Hostility/Aggression SMQ in the 18-study cohort. The estimates for RR and RD for varenicline vs placebo during treatment, per 100 subject-years were 1.10 (95% CI 0.60, 2.00) and 0.17 (95% CI -0.94, 1.29) and are shown in Figure 12 and Figure 13 respectively.

Figure 12. Risk Ratios (95% CI) of Incidence Rates for Hostility/Aggression SMQ During Treatment; 18-Study Cohort



MedDRA (v16.0) coding dictionary applied.
During Treatment Includes Data Up to 30 Days After the Last Dose of Study Drug.
Heterogeneity: Q = 4.72, df = 6, P = 0.5805, I_SQ = 0.0%.
IR = Incidence Rate per 100 Subject-Years (SY), NA = Not applicable (zero events in at least one group).
Mantel-Haenszel Model With Weights = Placebo Events * Varenicline Exposure/Total Exposure.
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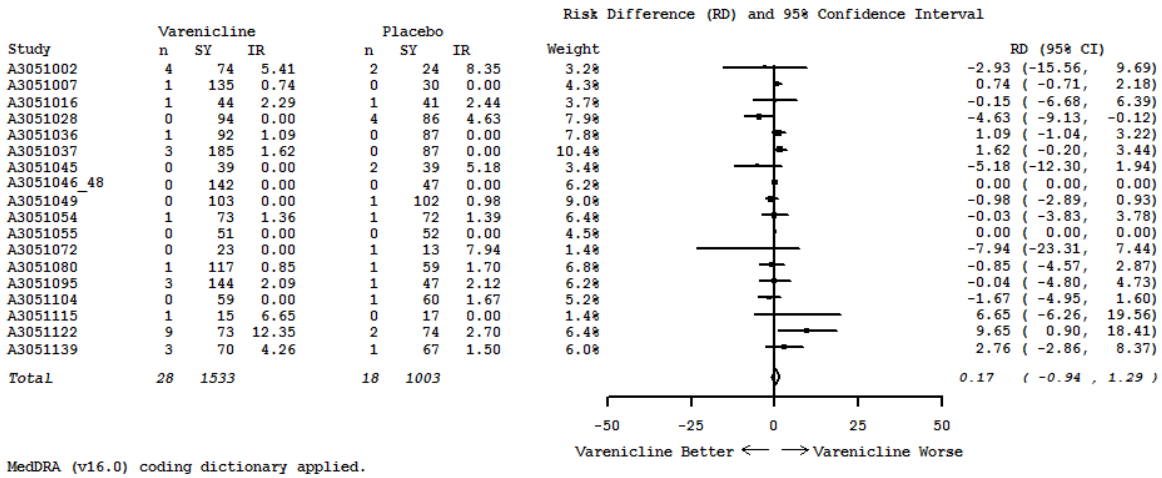
Figure 13. Subjects Reporting Treatment-Emergent AEs Coding to the: Risk Difference (95% CI) of Incidence Rates for Hostility/Aggression SMQ During Treatment – 18-Study Cohort



MedDRA (v16.0) coding dictionary applied.
During Treatment Includes Data Up to 30 Days After the Last Dose of Study Drug.
Heterogeneity: Q = 20.76, df = 17, P = 0.2374, I_SQ = 18.1%.
IR = Incidence Rate per 100 Subject-Years (SY).
Mantel-Haenszel Model With Weights = 1/Varenicline Exposure + 1/Placebo Exposure.
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Because the estimates for RR in the Depression Study (A3051122) and the Re-treatment Study (A3051139; study in subjects who had previously taken varenicline and either succeeded in quitting smoking but relapsed or who had failed to quit with their previous varenicline treatment) were relatively larger than in other studies (Figure 12) and the CI for

the RD in the Depression Study did not include 0 (Figure 13), the hostility/aggression events reported in these 2 studies were explored in further detail.

In the Depression study there were 9 varenicline subjects and 2 placebo subjects who reported AEs that coded to PTs in the Hostility/Aggression SMQ. One case coded to Sexual abuse, in which the varenicline subject was the victim of a sexual assault; this case was not further analyzed. The PTs reported in the other 8 varenicline and 2 placebo subjects were: Anger (1 varenicline subject and 0 placebo subjects), Aggression (2 varenicline subjects and 1 placebo subject), Hostility (5 varenicline subjects and 1 placebo subject). All of these events were mild or moderate in severity and none of the subjects discontinued treatment or the study due to these AEs. Seven of the 8 varenicline subjects had reduced their cigarette smoking prior to the AE (2 had quit entirely) while neither of the placebo subjects had reduced smoking. Of note, the AEs related to hostility/aggression in 5 of the 8 varenicline subjects and both of the 2 placebo subjects were solicited AEs from the interview utilized in the Depression study. The Depression study was the only study among the 18 studies in the meta-analysis to use this additional interview. The AEs of Hostility were further reviewed. For varenicline, 3 of the cases were mild and two moderate while the placebo case was mild. The onset of the first occurrence did not show a particular pattern in time: in the first 2 weeks of treatment for 2 varenicline subjects, after more than 4 weeks of treatment for two other varenicline subjects and after the treatment discontinuation for the fifth varenicline subject and for the placebo subject. For one of the varenicline subjects the investigator attributed causality to family problems. Two other varenicline subjects and the placebo subject had a past history of substance or alcohol abuse.

In the Re-treatment Study there were 3 varenicline subjects and 1 placebo subject who reported AEs that coded to PTs in the Hostility/Aggression SMQ. The PTs reported were: Anger (2 varenicline subjects and 1 placebo subject) and Aggression (1 varenicline subject and 0 placebo subjects). All AEs were mild or moderate in severity. Two of the varenicline treated subjects discontinued treatment and the study drug dosing was reduced in the placebo subject due to these AEs. Two of the varenicline subjects and the placebo subject had quit smoking or significantly reduced their smoking prior to the events. The remaining varenicline subject had no reduction in smoking.

In summary, the analysis of the aggressive behavior/hostility TEAEs in the 18-study cohort showed comparable results between varenicline and placebo (RR 1.10 (95% CI 0.60, 2.00).

5.3.2.2.3.3. Psychiatric Disorders SOC; 18-Study Cohort

All TEAEs that coded to the Psychiatric disorders SOC were reviewed. There were 1,534/5,072 (30.2%) varenicline subjects and 730/3,449 (21.2%) placebo subjects reporting AEs coding to the entire SOC. In contrast, 593/5,072 (11.7%) varenicline subjects and 388/3,449 (11.2%) placebo subjects reported AEs other than those coding to the HLGT Sleep disorders and disturbances. The number of subjects reporting AEs that coded to each of the HLGTs within the Psychiatric disorders SOC, as well as the incidence and RR (per 100 subject-years) is presented in Table 10.

Nearly all RRs except for the Sleep disorders and disturbances HLGT were associated with 95% CIs including 1. The exception was the RR for the Suicidal and self-injurious behaviors NEC HLGT which was 0.39 (95% CI: 0.16, 0.97) for varenicline vs placebo.

There was little or no evidence of heterogeneity, p-values for the differences of RRs/RDs between studies were >0.05, except for sleep disorders and disturbances (p<0.02).

Because sleep disorders are known to be associated with varenicline[33], the data for subjects who reported AEs that coded to the Psychiatric disorders SOC excluding Sleep disorders and disturbances HLGT events were further reviewed. The RR for varenicline vs placebo, per 100 subject-years, for subjects reporting at least 1 psychiatric AE other than those related to sleep was 1.01 (95% CI: 0.89, 1.15) as shown in Table 10, with an RD of 0.44 (95% CI: -4.28, 5.16). An analysis of the same data but restricted to those AEs with a severity rating of moderate or severe (as determined by the Investigator) also showed comparable rates between varenicline and placebo (RR per 100 subject-years=0.90[95% CI: 0.74, 1.09], RD=-1.85 [95% CI: -5.20, 1.50]).

Table 10. Incidence and Risk Ratio (per 100 subject-years) of HLGTs in the Psychiatric Disorders SOC, 18-Study Cohort

HLGT in Psychiatric disorders SOC	Varenicline (N=5,072) n (%)[a]	Placebo (N=3,449) n (%)[a]	Risk Ratio (95% CI)
Adjustment disorders (including subtypes)	1 (<0.1)	2 (0.1)	N/A
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)	0.84 (0.70, 1.02)
Changes in physical activity	46 (0.9)	31 (0.9)	0.86 (0.53, 1.40)
Cognitive and attention disorders and disturbances	2	2 (0.1)	N/A
Communication disorders and disturbances	1	1	N/A
Deliria (including confusion)	4 (0.1)	2 (0.1)	N/A
Dementia and amnestic conditions	0	0	N/A
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)	1.14 (0.90, 1.45)
Developmental disorders NEC	0	0	N/A
Dissociative disorders	8 (0.2)	5 (0.1)	0.54 (0.16, 1.84)
Disturbances in thinking and perception	21 (0.4)	10 (0.3)	1.28 (0.57, 2.85)
Eating disorders and disturbances	1	0	N/A
Impulse control disorders NEC	0	0	N/A
Manic and bipolar mood disorders and disturbances	4 (0.1)	1	N/A
Mood disorders and disturbances NEC	116 (2.3)	53 (1.5)	1.28 (0.93, 1.77)
Personality disorders and disturbances in behaviour	23 (0.5)	9 (0.3)	2.15 (0.98, 4.73)
Psychiatric and behavioural symptoms NEC	1	2 (0.1)	N/A
Psychiatric disorders NEC	24 (0.5)	19 (0.6)	0.91 (0.51, 1.62)
Schizophrenia and other psychotic disorders	2	1	N/A
Sexual dysfunctions, disturbances and gender identity disorders	29 (0.6)	17 (0.5)	1.10 (0.60, 2.02)
Sleep disorders and disturbances	1222 (24.1)	468 (13.6)	1.72 (1.54, 1.92)
Somatoform and factitious disorders	0	1	N/A
Suicidal and self-injurious behaviours NEC	9 (0.2)	13 (0.4)	0.39 (0.16, 0.97)
Any AE in the Psychiatric SOC other than those in the Sleep disorders and disturbances HLGT	593 (11.7)	388 (11.2)	1.01 (0.89, 1.15)

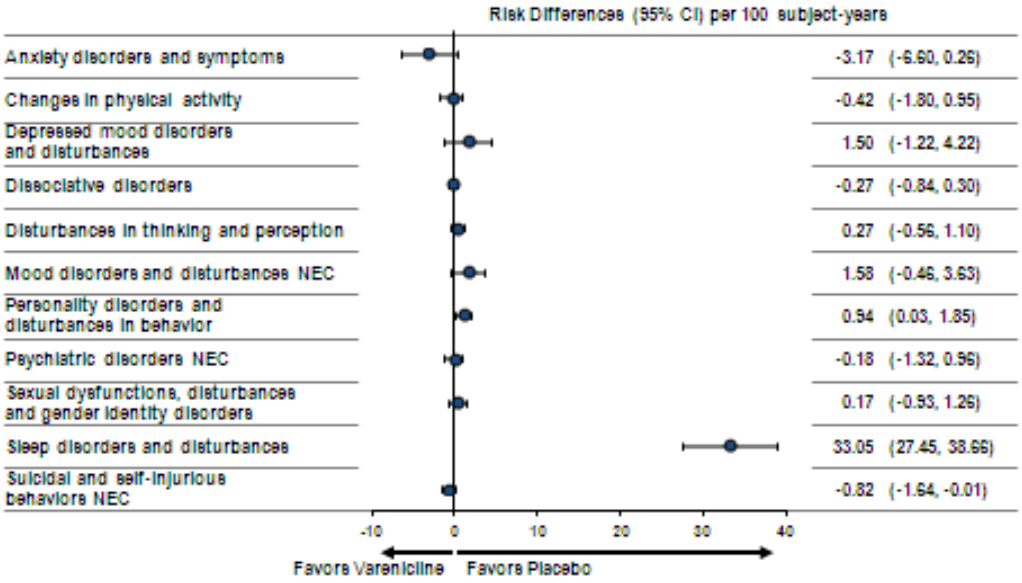
a. n represents number of subjects with treatment-emergent adverse events in the HLGT. % represents raw percentages, not weighted by number of subjects in each study, percentage was not calculated where event

Table 10. Incidence and Risk Ratio (per 100 subject-years) of HLGTs in the Psychiatric Disorders SOC, 18-Study Cohort

numbers are low
N/A – due to low number of events, RRs were not calculated.
MedDRA v 16.0

The RDs per 100 subject-years are presented for the HLGTs in the Psychiatric Disorders SOC for which there were sufficient events to conduct the analysis Figure 14.

Figure 14. Subjects with Treatment-Emergent AEs Coding to High Level Group Terms within the Psychiatric Disorders System Organ Class: Risk Differences (95% CIs) per 100 Subject-Years; 18-Study Cohort



The RDs for HLGTs in the Psychiatric disorders SOC other than those related to sleep showed a small number of events, either in excess for placebo (up to 3.2 events per 100 subject-years, reported for Anxiety disorders and symptoms) or in excess for varenicline (up to 1.6 events per 100 subject-years, reported for Mood disorders and disturbances), with associated 95% CIs including 0. There were two exceptions. One was for the Suicidal and self-injurious behaviors NEC HLGT for which the upper bound of the 95% CI was -0.01 showing 0.82 less events per 100 subject years for varenicline compared to placebo. The second was the Personality disorders and disturbances in behaviour HLGT for which the lower bound of the 95% CI was 0.03 and showed an excess of 0.9 events per 100 subject-years in the varenicline group. Table 11 shows the PTs in the Personality disorders and disturbances in behavior HLGT that were reported and the severity ratings for each PT. The PTs Aggression and Hostility are also contained within the Hostility /Aggression SMQ, the analysis of which showed no difference between varenicline and placebo (see Section 5.3.2.2.3.2). The other PTs reflect clinically diverse conditions, were characterized by a small number of subjects reporting each PT (1 or 2 subjects) and were mild in severity, as

rated by the Investigator (with one exception of a moderate AE of Paranoia in a varenicline subject). The conditions reflected by these PTs were clinically diverse and characterized by a small number of subjects reporting each PT (1 or 2 subjects). An analysis of the HLGT but restricted to those AEs with a severity rating of moderate or severe, as determined by the Investigator (12/23 varenicline subjects and 4/9 placebo subjects) yielded a RR per 100 subject-years of 2.25 (95% CI: 0.71, 7.17) and RD of 0.47 (95% CI: -0.15, 1.10).

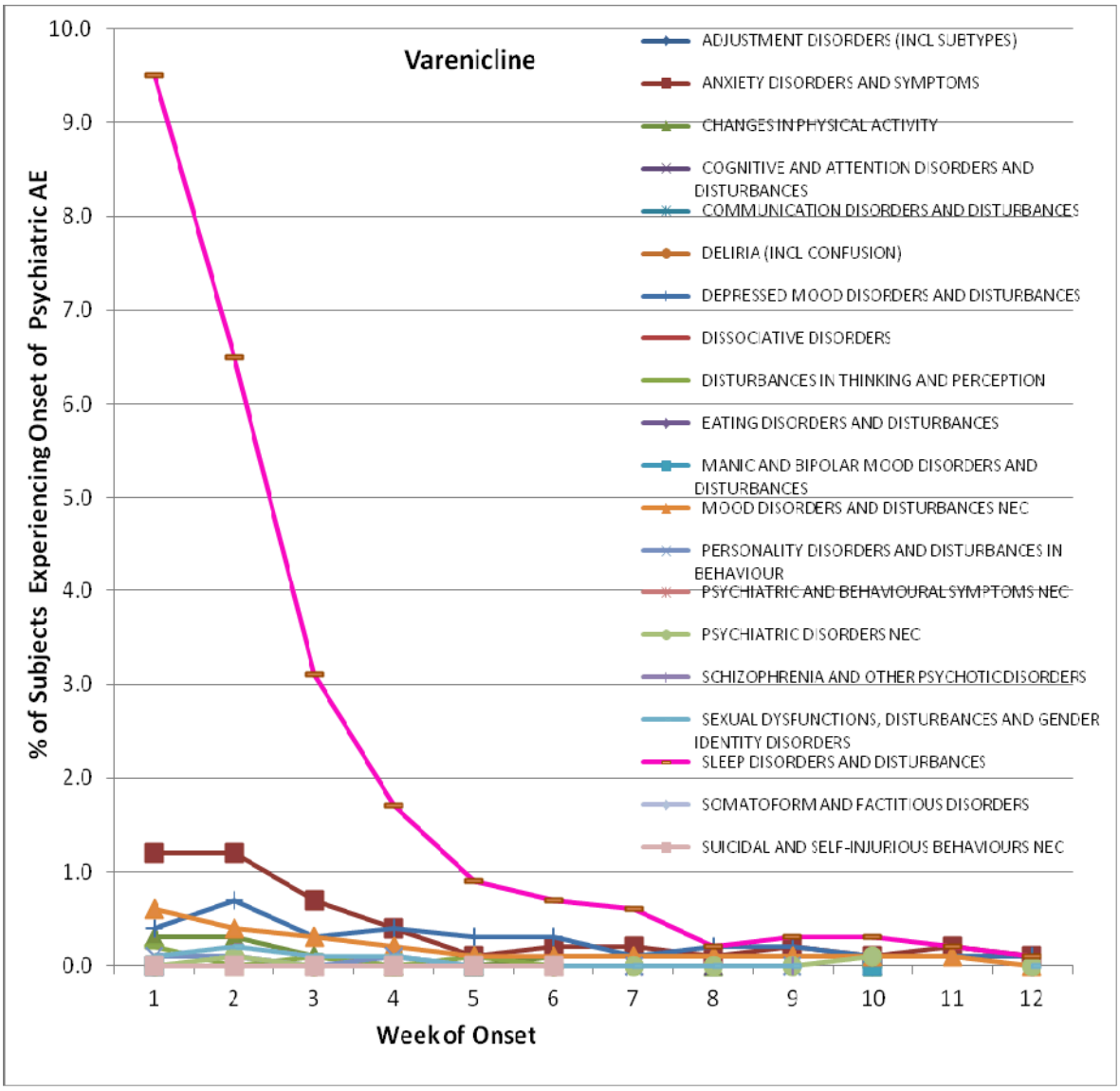
Table 11. Preferred Terms in the Personality Disorders and Disturbances in Behavior HLGT by Severity; 18-Study Cohort

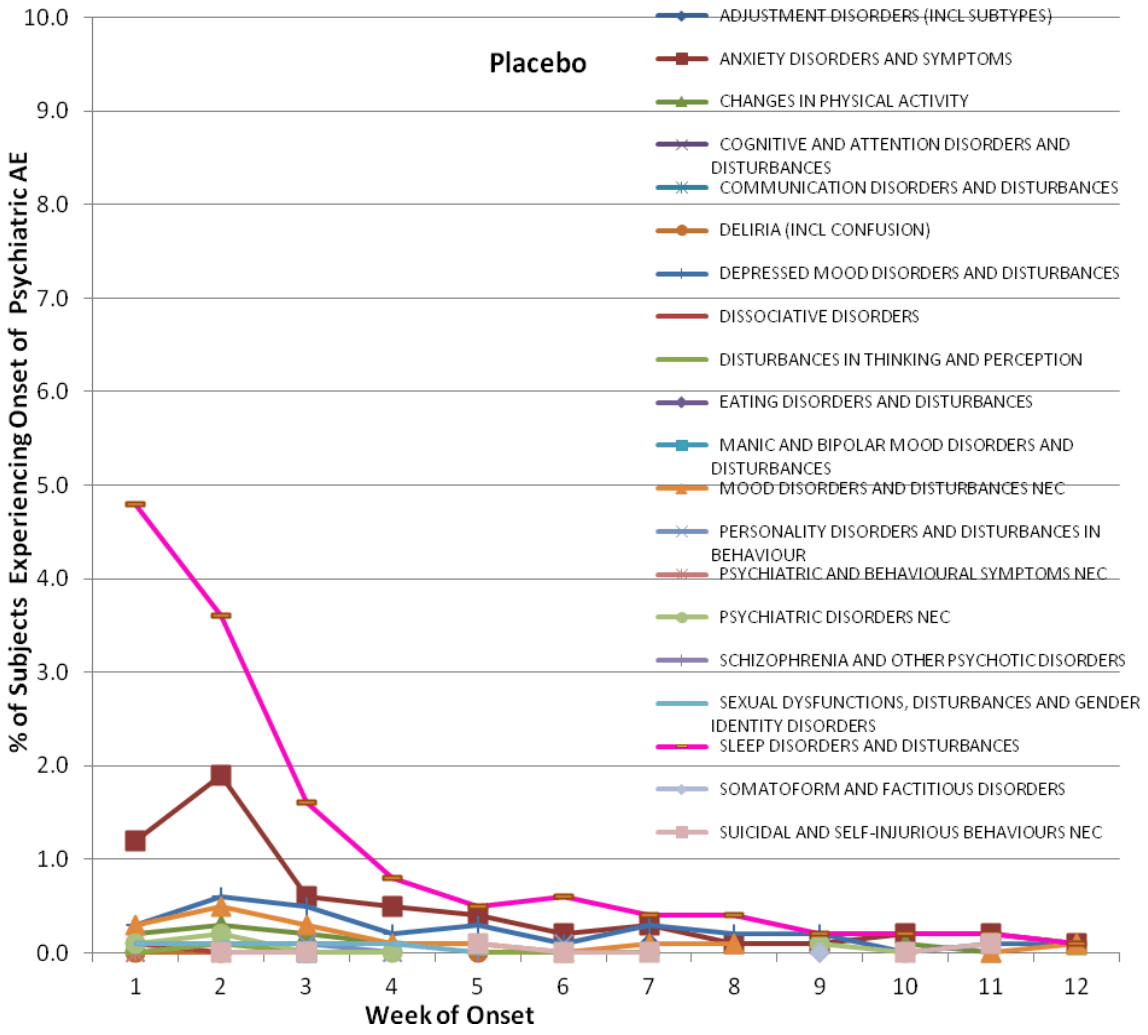
	Varenicline N=5,072 n (%)				Placebo N=3,449 n (%)			
HLGT PT	**Total**	**Mild**	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**
Personality disorders and disturbances in behavior	**23 (0.5)**				**9 (0.3)**			
Aggression	**10 (0.2)**	3	7	0	**6 (0.2)**	2	3	1
Grandiosity	**1 (<0.1)**	1	0	0	**0**	0	0	0
Hostility	**6 (0.1)**	3	3	0	**1 (<0.1)**	1	0	0
Impatience	**1 (<0.1)**	1	0	0	**1 (<0.1)**	1	0	0
Indifference	**0**	0	0	0	**1 (<0.1)**	1	0	0
Overconfidence	**1 (<0.1)**	1	0	0	**0**	0	0	0
Paranoia	**2 (<0.1)**	1	1	0	**0**	0	0	0
Personality disorder	**1 (<0.1)**	0	1	0	**0**	0	0	0
Social avoidant behavior	**1 (<0.1)**	1	0	0	**0**	0	0	0

HLGT=High Level Group Term; PT=Preferred Term.

Figure 15 shows the time to onset of psychiatric AEs (presented at the HLGT level) by study week. Data are presented separately for varenicline and placebo subjects.

Figure 15. Percent of Subjects with Onset of Psychiatric Adverse Events by Week for Varenicline and Placebo Subjects; 18-Study Cohort





Sleep-related AEs showed a higher rate of onset in varenicline subjects compared to placebo subjects during the first 4 to 5 weeks of treatment, after which time the onset rate was similar in the 2 treatment groups. AEs coding to all other psychiatric HLGTs showed similar rates of onset between varenicline and placebo, except for a small difference in anxiety-related events in Week 2, with the rate being lower in the varenicline compared to placebo. Some of the other psychiatric AEs showed small elevations in reporting rates over the first 3 weeks. The timing of the peaks in event onsets coincides with the period of time during which nicotine withdrawal symptoms would be expected to occur (see Section 3.2).

5.3.2.2.4. 5-Study and the 18-Study Meta-Analyses Summary and Conclusions

The RR of suicidal ideation and/or behavior reported on C-SSRS during the treatment period for varenicline vs placebo per 100 subject-years in the 5-study cohort was 0.79 (95% CI 0.46, 1.36). This analysis and similar analyses for suicidal ideation separately or for the entire study period for the 5-study cohort resulted in estimates for the RRs ranging from 0.79 to

1.15 (all 95% CIs included 1). The results showed no increased risk, compared to placebo, for suicidal ideation and/or behavior with varenicline use. The analysis of the Suicide/Self injury SMQ in the 18-study cohort also showed comparable results between varenicline and placebo.

The RR of TEAEs in the Hostility/Aggression SMQ for varenicline versus placebo, per 100 subject-years in the 18-study cohort was 1.10 (95% CI 0.60, 2.00) showing similar risk for the 2 treatment groups.

The review of the HLGTs within the Psychiatric Disorders SOC showed an increase in the HLGT Sleep disorders and disturbance for varenicline versus placebo; sleep-related AEs are known to be associated with varenicline treatment. The RR for the overall Psychiatric disorders SOC, excluding events in the Sleep disorders and disturbances HLGT, for varenicline vs placebo, per 100 subject-years, was 1.01 (95% CI: 0.89, 1.15). When only moderate and severe AEs were considered, the RR was 0.90 (95% CI: 0.74, 1.09), demonstrating a similar degree of risk between varenicline and placebo. The most frequent AEs in both treatment groups were related to sleep, anxiety, and depressed mood, which are common nicotine withdrawal symptoms.

These results from meta-analyses of placebo-controlled clinical trials do not show evidence of an increased risk of NPS events in varenicline-treated subjects compared to placebo-treated subjects.

5.3.2.3. Studies Assessing Nicotine Withdrawal

Many of the NPS AEs reported in the 18 placebo-controlled studies correlate with the known symptoms of nicotine withdrawal, ie, irritability, frustration or anger, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood and insomnia.[22] Nicotine withdrawal symptoms were assessed in 2 different analyses, 1 using pooled Minnesota Nicotine Withdrawal Scale (MNWS) data and the other using psychiatric scale and AE data in a study in which abstinence was enforced in both the varenicline and placebo groups. These analyses are described below.

5.3.2.3.1. Minnesota Nicotine Withdrawal Scale 8-Study Combined Analysis

The MNWS has been shown to be a valid and reliable measure of nicotine withdrawal symptoms[34,35;36] and is the most often used scale[37]. A combined analysis of MNWS pooled data from 8 studies of similar design, which administered the MNWS in a comparable way, was performed[38] The 8 studies included in the pooled analysis of MNWS data were studies A3051002, A3051007, A3051016, A3051028, A3051036, A3051045, A3051046, and A3051115. (see Table 3 and Table 18 for brief study descriptions).

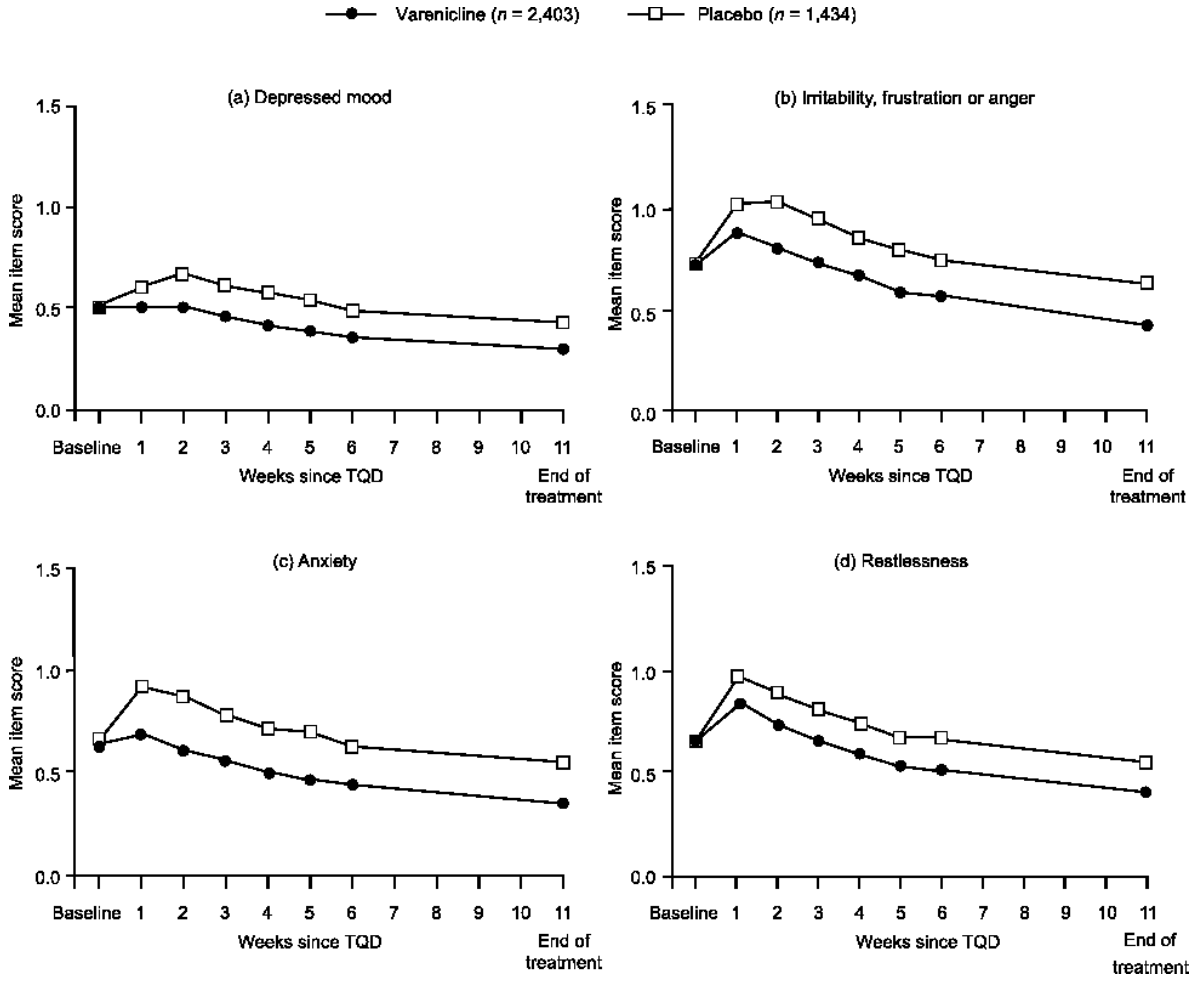
The MNWS used in each of these studies instructed participants to rate on a scale of 0–4 the degree to which they had been feeling a number of symptoms over the previous 24 hr. A mixed model for repeated measures analysis controlling for baseline score, treatment, visit, and treatment by visit interaction was performed for each MNWS item to compare results for

varenicline- and placebo-treated participants at each visit (Weeks 1–6 and 11 after the target quit date [TQD]).

Results of MNWS Analysis

Analysis of MNWS scores showed that the ratings for the NPS symptoms of depressed mood; irritability, frustration, or anger; anxiety; and restlessness, as shown in Figure 16 a–d, peaked during the first or second week after the TQD, before gradually returning to baseline levels at Week 5 or 6 for placebo-treated participants, and earlier for varenicline. For all these items, scores were significantly lower ($p < .01$) for varenicline than placebo at each of Weeks 1–6 and Week 11 after the TQD.

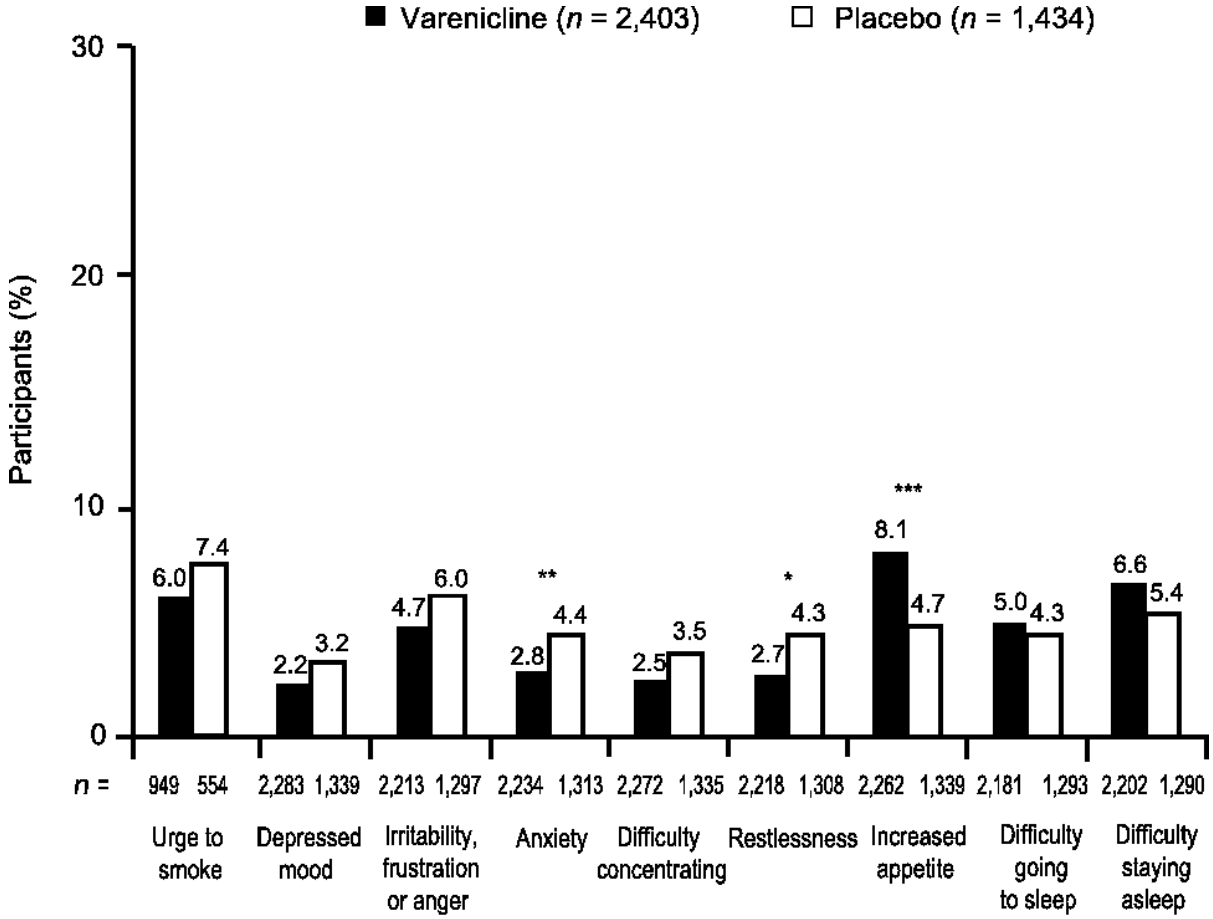
Figure 16. NPS Nicotine Withdrawal Symptoms as Captured by the MNWS 8-Study Meta-Analysis



Mean ratings of (a) depressed mood; (b) irritability, frustration, or anger; (c) anxiety; and (d) restlessness by treatment condition and weeks after target quit date (TQD). Significant difference (a, $p < .01$; b, $p < .001$; c and d, $p < .0001$) between varenicline and placebo at Weeks 1–6 and 11 post-TQD.
Figure based on observed mean values; statistical analysis based on multivariate repeated measures model controlling for baseline, visit, treatment, and treatment by visit interaction. *n* values are from the ITT population and do not represent those used in the repeated measures model.

Marked increases in symptom severity ratings (from 0–2 at baseline to 4 at any follow-up visit) for the 5 NPS symptoms (depressed mood, irritability, anxiety, difficulty concentrating, and restlessness) and urge to smoke were less frequent on varenicline than on placebo (Figure 17). The only symptom for which there was a significantly higher frequency of marked increases in severity with varenicline vs placebo was increased appetite.

Figure 17. Changes in the Severity of MNWS Scores from Baseline



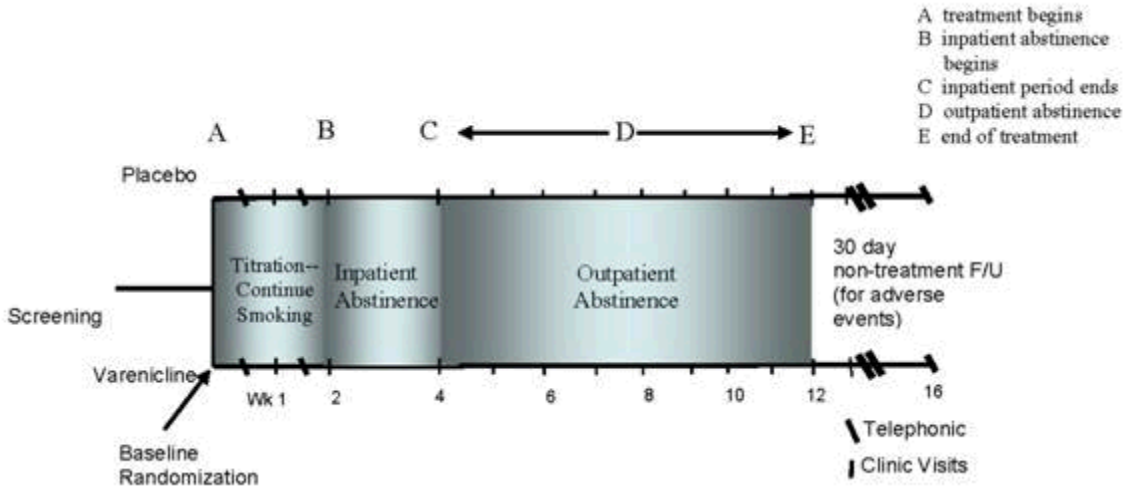
Percentage of participants who had a Minnesota Nicotine Withdrawal Scale item score of 0–2 at baseline and a score of 4 (extreme) at any follow-up. n = number of subjects who had MNWS item score of 0, 1, or 2 at baseline and had at least one postbaseline assessment. *p = .0113; **p = .009; ***p < .0001 based on the chi-square test.

5.3.2.3.2. Enforced Abstinence Study

Study A3051115 (the Enforced Abstinence Study) was a randomized, double-blind, pilot study designed to evaluate rates of NPS and assess neuropsychiatric status in smokers quitting smoking on either varenicline or placebo. At study initiation, 110 smokers were randomly assigned in a 1:1 ratio to receive either varenicline or placebo for a 12-week treatment period. Post-treatment follow-up extended out 4 additional weeks. A 2-week inpatient treatment period was included to enforce abstinence in both groups, in an effort to

minimize the potential for differential impact of nicotine withdrawal symptoms on neuropsychiatric status. The treatment and monitoring periods are displayed graphically below.

Figure 18. Study Design: Enforced Abstinence Study (A3051115)



The key inclusion criterion for the study was a Fagerström Test for Nicotine Dependence (FTND) score >5 (indicating moderate or greater nicotine dependence) and key exclusion criteria included current or past psychiatric history, past suicidal ideation or behavior, current depression, and current anxiety. Most subjects in this study were males; the average age was 33, with an average 22 cigarettes/day smoked, and a FTND score >7.

AE data was collected throughout the 16-week study period. In addition, during treatment, validated NPS assessment scales were used to collect further information about neuropsychiatric status. These included: (1) MADRS (depression); (2) HAM-A (anxiety); (3) OAS-M (aggression, irritability and suicidality); (4) POMS (mood and affective states); and (5) C-SSRS (suicidality). MADRS, HAM-A, OAS-M and C-SSRS (except weeks 3 and 4) were administered weekly; POMS was administered daily, while the Social Dysfunction and Aggression Scale was completed 3 times a day during inpatient treatment only.

Neuropsychiatric Adverse Events: The frequency of NPS AEs reported during the study was similar between the varenicline and placebo groups, with the exception of Insomnia and Somnolence, which were reported at higher rates in the varenicline group. NPS AEs included: Irritability (30.9% vs. 30.9%), Agitation (0% vs. 3.6%), Anxiety (10.9% vs. 12.7%), Restlessness (5.5% vs. 3.6%), Depressed mood (9.1% vs. 7.3%), Depression (1.8% vs. 1.8%), and Aggression (1.8% vs. 0%). No events of suicidal ideation and/or behavior were reported in the trial.

Neuropsychiatric Scales: During the full treatment period, no significant differences were seen between treatment groups in *depressive symptoms* (MADRS, TD = 0.03, 95% CI: -0.68—0.73; NS); *anxiety symptoms* (HAM-A, TD =0.14, 95% CI:-0.62—0.90; NS); *aggression* (OAS-M, TD=0.5, 95% CI: -1.18—2.18; NS); *irritability* (OAS-M, TD = 0.08,

95% CI: -0.17—0.34; NS); *suicidality* (OAS-M, no varenicline patients had a score above zero (no ideation); *total mood disturbances* (POMS, TD = 0.5, 95% CI: -0.52—1.53; NS); *tension/anxiety* (POMS, TD = 0.44, 95% CI: -0.18—1.06; NS); and *depression/dejection* (POMS, TD = 0.43, 95% CI: -0.19—1.05, NS). A small, statistically significant increase was observed in the POMS anger/hostility subscale (TD = 0.83, 95% CI: 0.14—1.52). There was no significant difference between treatment groups in the mean change from baseline in the Social Dysfunction and Aggression Scale score (TD = -0.07, 95% CI: -0.26—0.11, NS, baseline to last assessment). Increases in measures of depression, anxiety and irritability were observed for both treatment groups during the inpatient treatment period (no significant differences between groups), and may have been related to the inpatient confinement. No patients receiving varenicline reported self-injurious behavior or suicidal ideation on C-SSRS.

5.3.2.3.3. Nicotine Withdrawal Assessments Summary and Conclusions

The MNWS data showed that use of varenicline does not increase, and actually significantly reduces NPS symptoms (such as depressed mood, irritability, frustration or anger, difficulty concentrating, anxiety, and restlessness) and urge to smoke. The Enforced Abstinence Study which aimed to remove any differential in the abstinence rate between treatment groups and control for nicotine withdrawal, did not demonstrate consistent differences in psychiatric rating scales between varenicline and placebo subjects.

5.3.2.4. Post Marketing Requirement Safety Study, A3051123

Pfizer is currently conducting a randomized, double-blind, active-and placebo-controlled study to compare the risk of clinically significant NPS events, including but not limited to suicidal ideation and behavior, in individuals using varenicline, bupropion, NRT, or placebo as aids to smoking cessation over 12 weeks of treatment. The study seeks to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant NPS events compared to individuals without prior history of psychiatric disorders while using each of the smoking cessation aids. The design of this study was agreed to with the FDA before study initiation. The study is designed to include a total of 8,000 smokers, 4,000 with no history of a psychiatric disorder and 4,000 with a history of a psychiatric disorder, as documented by the SCID at screening. Subjects in the study are randomized within each of these cohorts to 1 of 4 treatment arms, varenicline, bupropion, NRT patch, or placebo. As a result, 1,000 subjects in each of the 2 cohorts (psychiatric history and no psychiatric history) will receive varenicline; each of the other 3 treatment arms will similarly have 1,000 subjects in each of the 2 cohorts. To allow comparisons among the treatment arms, the study employed a triple-dummy design, ie, all 4 treatments are blinded, and each subject will receive all 4 treatments, but of these, only 1 will be active and 3 will be placebos. The primary endpoint is a composite of NPS AEs, which is defined as the number of subjects reporting at least 1 treatment-emergent “severe” AE of anxiety, depression, feeling abnormal, or hostility, and/or the occurrence of at least 1 treatment-emergent “moderate” or “severe” AE of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. Subjects will be treated for 12 weeks and followed for an additional 12 weeks. Similar to other varenicline trials, all subjects will receive brief

smoking cessation counseling at each study contact, and efficacy will be measured as CO-confirmed continuous abstinence rates from Weeks 9 to 12 and 9 to 24.

Study A3051123 recently completed enrollment, with last subject last visit expected by the end of 2014, and a final clinical study report expected in 3rd quarter 2015.

5.3.2.5. Literature Review of Non-Pfizer Randomized, Controlled Clinical Trials Reporting on NPS Events

A literature search to identify double–blind, randomized, controlled trials or meta-analyses of randomized, controlled trials that reported NPS safety results for varenicline vs placebo or another comparator was conducted. The following databases were searched (using a cut-off date of 25 February 2014) for varenicline and various NPS keywords and mental disorders subject headings: Ovid Medline, Embase, Embase Daily Alerts and Derwent Drug File. The search terms were based on NPS terms that are included in the US CHANTIX label and included: psychiatric, neuropsychiatric, mental disorders, suicide, suicidal ideation, suicidal behavior, suicide attempt, self harm, depression, depressive disorder, depressed mood, mood disorder, schizophrenia, hallucination, delusion, psychosis, paranoia, mania, bipolar disorder, anxiety, panic, agitation, aggression, hostility, abnormal behavior, abnormal thinking, and personality disorder. Preclinical publications, conference literature, and other publication types such as notes, comments, editorials and non-English language publications were excluded during the search process. Studies in non-smokers, populations using varenicline for indications other than smoking cessation, studies in which all patients received varenicline, studies of less than 20 patients treated with varenicline and publications not reporting original data (such as review articles) were excluded during the review of the search results.

The review of the literature identified 10 relevant publications matching the search objective. Of these 10 publications, 4 publications included results from 3 meta-analyses (2 publications reported on the same Cochrane meta-analysis) and 6 were clinical trials. Only NPS results were summarized below for these 9 publications.

The 3 meta-analyses (Cahill, Gibbons, Huang), found no evidence of increased NPS risk with varenicline when compared with placebo.

The first meta-analysis (Cahill[39,40]) was based on 14 varenicline double-blind, randomized, controlled trials (of which 13 were Pfizer sponsored) and included 3,984 varenicline and 2,349 placebo patients. The subgroup analysis of NPS SAEs yielded an RR of 0.53 (95% CI: 0.17 – 1.67) for varenicline vs placebo.

The second meta-analysis (Gibbons et al[41]) studied the NPS safety of varenicline using person level AE data from 17 randomized placebo-controlled trials (4,823 varenicline and 3204 placebo patients) of varenicline conducted by Pfizer. The results revealed the overall effect of varenicline on suicidal thoughts and behavior (odds ratio (OR): 0.57; 95% CI: 0.23-1.38), depression (OR: 1.01, 95% CI: 0.68-1.52), and aggression/agitation (OR=1.27, 95% CI: 0.85–1.92) was not significant. Psychiatric illness did not moderate the effect of

varenicline for any of these symptoms. Having a current or past psychiatric illness increased the risk of NPS events equally in varenicline treated and placebo patients.

The third meta-analysis (Huang et al[42]) included 10 randomized controlled varenicline trials (6,375 smokers), all conducted by Pfizer. The analysis found there was not sufficient evidence that varenicline was associated with an increased risk of psychiatric AEs compared with placebo (RR: 1.45, 95% CI: 0.90-2.32).

Of the 6 clinical trial publications, 2 publications involved patients with psychiatric co-morbidities. The first study (Evins et al[43]) was a randomized, double-blind, placebo-controlled, relapse–prevention trial in smokers with schizophrenia or bipolar disorder. In the open-label phase, 203 smokers received 12 weeks varenicline. At Week 12, 87/203 (43%) subjects had 2 weeks or more of continuous abstinence and were randomized to varenicline or placebo from Weeks 12-52. The study utilized psychiatric scales, including the Brief Psychiatric Rating Scale (BPRS) and Calgary Depression Scale for Schizophrenia and found there was no effect of treatment assignment on severity of psychiatric symptoms. Although the study was not powered to detect changes in psychiatric symptoms, the authors stated "…we detected no signal for varenicline to be associated with new or worsening neuropsychiatric symptoms". The second study (Hong et al[44]) was a double-blind, randomized, placebo-controlled trial of smokers and non-smokers with schizophrenia or schizoaffective disorders that evaluated the effects of varenicline on neurobiological and cognitive biomarkers. The study included a total of 69 smokers and non-smokers and utilized several psychiatric scales. With regards to the BPRS total, there were no significant treatment or interaction effects with a trend towards reduced psychiatric symptoms for varenicline vs placebo ($F_{1,54.2} = 3.32$, $p=0.07$). The BPRS psychosis subscale showed a trend towards reduced psychosis in the varenicline group compared to the placebo group ($F_{1,58} = 3.89$, $p=0.053$). There were no differences in treatment effects in smokers vs non-smokers (all $p \geq 0.30$). There were no significant effects of treatment on negative symptoms assessed using the Schedule for Assessment of Negative Symptoms, or on depression, which was assessed using the HAM-D. Assessments of depression, anxiety and suicidality were further probed via Item 3 of HAM-D (suicidality), Item 13 of the BPRS (depression) and the BPRS anxiety rating; all of which showed no treatment effect. Hence, there was no evidence that treatment with slowly titrated varenicline at 1 mg/day increased any of these measures.

In the remaining 4 clinical study publications, 2 (McClure, Steinberg) involved comparisons of varenicline to placebo and 2 (Stein, Cincirpini) involved an active comparator as well. These studies ranged in size from 47 to 315 subjects. Of these 4 studies, Cinciripini et al[45] used several psychiatric scales including the Positive and Negative Affect Schedule, Wisconsin Smoking Withdrawal Scale, and the Center for Epidemiological Studies Depression Scale. The study specifically examined the effect of varenicline vs bupropion SR on smoking cessation and emotional functioning. The study found that varenicline use was associated with a generalized suppression of depression when compared with the other treatments, while both bupropion and varenicline improved concentration and decreased negative affect and sadness when compared with placebo, while having little effects on anxiety and anger. In addition, no significant differences were noted for any of the psychiatric or neurological AEs between treatment arms. The second study (Stein[46]) compared varenicline, NRT and placebo for smoking cessation in methadone maintained

smokers and reported that smokers on varenicline tended to be less likely to report anger, irritability, frustration or anxiety related events during the initial month of treatment. Two participants in the varenicline arm stopped study medication due to neurobehavioral adverse effects. The third study (Steinberg[47]), which compared varenicline vs placebo in hospitalized smokers, reported at a 4-week outpatient follow-up visit of a decrease in MNWS of 1.45 points in the varenicline group compared with a 0.11 increase in the placebo group, this difference was not statistically significant. Depression was reported in 5 patients in both groups, which was not a statistically significant difference. The fourth study (McClure[48]) compared the relapse prevention effects of varenicline vs placebo following a programmed lapse, which occurred on the second day of the quit attempt. This study reported that subjective assessments measured on withdrawal (MNWS) and mood (PANSS) were not sensitive to medication effects but showed an effect of time, with ratings decreasing over time in both groups.

5.3.2.5.1. Literature Review Summary and Conclusions

The review of the literature identified 3 meta-analyses and 6 double-blind, randomized, controlled trials that reported on NPS safety for varenicline when used in smokers. None of these publications reported evidence of an increased NPS risk with varenicline.

5.3.3. Current Publically Reported Observational Studies

As noted in Table 2, there were no population-based observational studies with a comparator published through 2009. Since 2009 several such studies have been publically reported.

5.3.3.1. Literature Search Methodology

Pfizer conducted a literature search to identify population-based observational studies assessing the risk of NPS events in varenicline users compared to users of other smoking cessation interventions.

Similar to the search for double-blind, randomized, controlled trials, the same databases were searched (using a cut-off date of 25 February 2014) for varenicline and various NPS keywords and mental disorders subject headings. The search terms were based on NPS terms that are included in the US CHANTIX label and are listed in Section 5.3.2.5. Observational studies without comparators, such as Prescription Event Monitoring studies, or those conducted at a single site (not population based) were excluded.

During the review of the search results, 4 publications of population-based observational studies comparing varenicline to another smoking cessation medication were identified after excluding review type of articles. Two of the publications, Gunnell[49] and Thomas[50], used the same data source, the Clinical Practice Research Datalink, previously called the General Practice Research Database. The Thomas publication builds upon the cohort in the Gunnell publication, nearly tripling the number of varenicline patients, and also links to an external mortality database to define the primary endpoint fatal and non-fatal self-harm, which was not done in the Gunnell study. Therefore only the results of the Thomas study are presented below. Details of the Gunnell study are provided in Appendix 6. In addition to the literature

search, Pfizer also became aware of the results of an unpublished retrospective cohort study conducted by the Department of Veterans Affairs (VA) to assess mental health hospitalizations in patients who received varenicline or nicotine replacement therapy, which were posted on 24 October 2011 at ://www.fda.gov/Drugs/DrugSafety/ ucm276737.htm#sa.[51] Pfizer did not have access to the full report, and therefore, only the main results that were included in the online posting are provided below.

The 4 observational cohort studies identified are summarized in Table 12 below. Each is described in detail in Section 5.3.3.2.1.

Table 12. Summary of Four Population-Based Observational Cohort Studies

Lead Author	Source Population	Study Period	Comparator	Primary Endpoint
Thomas	UK general practice	01Sep06 to 31Oct11	NRT	Fatal or non-fatal self-harm Pharmacologic treatment for depression
Pasternak	Population of Denmark	01Jan07 to 31Dec10	Bupropion	ED visit or inpatient admission for a psychiatric diagnosis within 30 days of treatment initiation
Meyer & final report to DoD	US Military Health System	01Aug06 to 31Aug07	NRT	Primary inpatient discharge diagnosis for an NPS condition within 30 days of treatment initiation
Department of Veterans Affairs	US Veterans Health Administration	01May06 to 30Sep07	NRT	Primary inpatient discharge diagnosis for an NPS condition within 30 days of treatment initiation

ED=emergency department; NRT=nicotine replacement therapy; UK=United Kingdom; US=United States; DoD=Department of Defense.

5.3.3.2. Population-Based Observational Study Results

The results of the 4 studies (3 publications and the unpublished VA study) noted above are summarized in Table 13 below.

Table 13. Summary of Primary Results from Four Population-Based Observational Cohort Studies with Comparators

Endpoint	Author	Varenicline # Events/ Sample Size	Comparator # Events/ Sample Size	Hazard Ratio	95% CI	
					Lower Limit	Upper Limit
Fatal Or Non Fatal Self Harm	Thomas	19 / 30,352	69 / 78,407	0.88	0.52	1.49
Pharmacological Treatment For Depression	Thomas	255 / 18,386	799 / 42,475	0.75	0.65	0.87

Table 13. Summary of Primary Results from Four Population-Based Observational Cohort Studies with Comparators

Endpoint	Author	Varenicline # Events/ Sample Size	Comparator # Events/ Sample Size	Hazard Ratio	95% CI	
					Lower Limit	Upper Limit
Hospitalized For NPS Condition	Meyer	16 / 10,814	14 / 10,814	1.14	0.56	2.34
	Dept Veterans Affairs	16 / 14,131	21 / 14,131	0.76	0.40	1.46
	Pasternak[a]	39 / 17,935	46 / 17,935	0.85	0.55	1.30

a. Includes hospitalizations and also emergency department visits for NPS conditions.

5.3.3.2.1. Review of Individual Observational Studies

Meyer TE, Taylor LG, Xie S, Graham DJ, Mosholder AD, Williams JR, Moeny D, Ouellet-Hellstrom RP and Coster TS. (2013), Neuropsychiatric events in varenicline and nicotine replacement patch users in the Military Health System. Addiction, 108: 203–210. doi: 10.1111/j.1360-0443.2012.04024.x [52]

Design: This retrospective cohort study within the Military Health System included new users of varenicline and NRT patch who filled a prescription from 01 August 2006 to 31 August 2007.

Outcomes: The main outcome investigated was a primary in-patient discharge diagnosis for a NPS condition. Secondary outcomes included NPS diagnosis in any diagnostic position during an in-patient stay and any NPS diagnoses in out-patient records that occurred twice on different days. Follow-up continued for 30 days after the prescription fill date with sensitivity analyses performed for 60 days after prescription was filled.

Results: There were 10,814 varenicline users and an equal number of NRT users in the propensity-matched analysis, which made the two cohorts more similar with respect to demographic, medical and pharmacy characteristics. Looking specifically at psychiatric history, 12% had a NPS diagnosis in the past year and ~35% had been dispensed between 1-7 psychiatric prescriptions in the previous year.

When followed for 30 days, varenicline users did not have a significantly increased rate of in-patient primary discharge NPS hospitalizations compared to NRT patch (varenicline 16/10,814 vs. NRT 14/10,814; HR=1.14, 95% CI: 0.56-2.34) when the 2 cohorts were balanced according to confounders. Results were similar when subjects were followed for 60 days (HR overall = 1.11, 95% CI: 0.59-2.10). When stratified by prior NPS history, crude HRs did not differ significantly (P-interaction = 0.79) between patients with (HR = 0.49, 95% CI: 0.27–0.89) or without (HR = 0.58, 95% CI: 0.18–1.83) a prior NPS diagnosis. Thirty day NPS event rates were lower among varenicline than NRT patch users for the

secondary outcomes of any NPS diagnoses during in-patient (HR = 0.79; 95% CI: 0.50-1.24) or outpatient encounters (HR= 0.71, 95% CI: 0.60-0.84).

Authors Conclusions: The authors concluded that there does not appear to be an increase in NPS hospitalizations with varenicline compared with NRT patch over 30 or 60 days after drug initiation.

Strengths and Limitations: Several limitations were identified by the authors. First, the secondary outcomes are more likely to suffer from misclassification as the NPS codes that are not in the primary position may indicate treatment for a co-morbid NPS condition. In the out-patient setting secondary outcome, it may represent routine psychiatric rather than an adverse NPS event. Second, misclassification of the outcome may differ by the system of care as would the propensity for receiving a certain drug. This potential bias was adjusted for by inclusion of an indicator of source of care in the past 365 days. Confounding due to known, unknown or unmeasured confounders may remain. Next, NPS events were identified by ICD-9 codes, which will not capture psychiatric episodes that result in medication discontinuation without a healthcare professional encounter. There may be instances where severe events such as successful suicide without hospitalization were not captured. Outcome definitions were not validated against medical records. Last, as this study was performed prior to the FDA communications regarding possible NPS events with varenicline, rates are expected to be equally under-ascertained in both cohorts with a bias towards the null.

The strengths of this study include the relatively large drug cohort sizes, the use of incident user cohorts which reduces the potential for survivor bias and the population-based sample. Additionally, the sample included patients with psychiatric disorders, unlike previous varenicline clinical trials, and a variety of NPS outcomes were evaluated. In addition as mental health services are free or available at very low cost in the Military Health System (MHS), less confounding by socio-economic factors or access to care may be present, and cost incentives encourage MHS beneficiaries to utilize the MHS system rather than go outside health coverage, maximizing the completeness of the outcome coverage.

Note: In addition to the publication summarized above, Pfizer had access to the full report of the study obtained via the Freedom of Information Act. The full report[53] provides other baseline characteristics not included in the Meyer publication regarding the varenicline and NRT groups as well as subgroup characteristics of those who experienced an NPS event and additional statistical analyses for the individual inpatient NPS diagnoses and NPS events that occurred within 60 days of starting therapy amongst others.

Pasternak B, Svanström H and Hviid A. (2013), Use of varenicline versus bupropion and risk of psychiatric adverse events. Addiction, 108: 1336–1343. doi: 10.1111/add.12165[54]

Design: By linking national registries in Denmark, this cohort study investigated whether varenicline was associated with an increased risk of psychiatric AEs compared with bupropion in patients who initiated use of these medications from 1 Jan 2007 to 31 Dec 2010.

Outcome: The primary outcome was any psychiatric AE (defined as an emergency department visit or in-patient admission with a psychiatric diagnosis) that had occurred within 30 days of therapy initiation. Data was analyzed in unmatched and propensity score matched cohorts.

Results: In the unmatched cohort, 59,790 and 17,936 new users of varenicline and bupropion, respectively, were identified. Baseline characteristics were similar between the two groups. The medical histories of psychiatric disorders that were reported were mood disorders (varenicline 4% vs. bupropion 5%), psychotic disorder (1% vs. 1%), neurotic stress related somatoform disorder (5% vs. 6%), substance abuse (6% vs. 7%), other psychiatric disorder (4% vs. 4%) and suicide attempt (<1% vs 1%). Overall, varenicline users were less likely to have a history of some psychiatric disorders. In this unmatched cohort, there were 106 (0.18%) psychiatric AEs among 59,790 varenicline users (rate 22 events per 1000 person-years), compared with 46 (0.26%) events among 17,936 bupropion users (31 per 1000); the hazard ratio (HR) was 0.69 [95% CI: 0.49–0.98].

In the propensity score-matched analysis, there were 17,935 varenicline users that were matched in a 1:1 ratio to bupropion users. As expected, all baseline characteristics including medical history of psychiatric disorder and use of psychiatric drugs in the last year were similar between the two groups. There were 39 (0.22%) events that occurred among 17,935 varenicline users (27 per 1000), compared with 46 (0.26%) events among 17,935 bupropion users (31 per 1000). There was no significant association between varenicline use and psychiatric AEs compared with bupropion (HR 0.85, 95% CI: 0.55–1.30). While the overall rate of psychiatric AEs was higher among participants with a history of psychiatric disorder, the risk associated with varenicline vs bupropion did not differ significantly by history of psychiatric disorder.

Authors Conclusions: In Denmark, the risk of psychiatric AEs diagnosed during an emergency department visit or in-patient admission was not significantly higher with varenicline use compared with bupropion use.

Strengths and Limitations: Several limitations were identified by the authors. First, drug use was based on filled prescription date assuming that the day when the drug was dispensed was the day when treatment was started. If participants started treatment later or did not start treatment at all, unexposed person-time would have been introduced. Although a range of potential confounders were controlled for by the use of propensity score-matching, the possibility of unmeasured confounding cannot be excluded. The use of an unexposed cohort would have introduced confounding by indication where effects of SC would not have been able to be separated from effects of treatment. Therefore, a comparison was made with bupropion, which has an identical indication. Bupropion also has a boxed warning related to NPS adverse events. In addition, no information on baseline level of smoking or smoking cessation rates was available; both factors could be related to the study outcome events. Because smoking abstinence might lead to exacerbation of symptoms from pre-existing psychiatric disorder, differential cessation rates between the two drugs might have influenced the results. Next, the secondary analyses of psychiatric events with follow-up at 90 and 180 days found protective associations in favor of varenicline. As the differences were small and because this was not the primary aim of the study, this finding was not viewed as evidence of

superiority. Another limitation though unlikely is that given the antidepressant effects of bupropion, it is possible that patients who wish to quit smoking and have symptoms of depression might be prescribed bupropion preferentially over varenicline. These patients may be more likely to present with psychiatric events at a later time-point. Also, comparison with bupropion provides a means to control for the influence from smoking cessation itself as it has the same indication. However, spontaneous reports indicate that bupropion may also be associated with psychiatric AEs and, accordingly, the product label carries a boxed warning alerting about this possibility. The last limitation is that although the propensity score-matched analysis included almost 18,000 participants in each exposure group, this sample size was too small to address the question of whether there is increased risk of suicide attempts and completed suicide.

Strengths of this study were it linked registries in Denmark. Due to the size of the study, estimates were precise and on the basis of the upper limit of the confidence intervals, it allowed for exclusion of more than a 30% increase risk associated with varenicline.

Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. BMJ 2013;347:f5704[50]

Design: Prospective cohort study conducted in the Clinical Practice Research Datalink (CPRD) to compare risk of suicide-related outcomes in patients prescribed varenicline or bupropion compared with those prescribed NRT from 01 September 2006 to 31 October 2011.

Outcome: The primary outcomes were incident episodes of depression as measured by the date that antidepressant treatment was initiated and by fatal and non-fatal self harm as measured by death from suicide in the Office for National Statistics (ONS) mortality database and a hospital admission for self-harm that occurred within 3 months of the first prescription.

Results: There were 119,546 patients identified for inclusion in the analysis: 81,545 were prescribed NRT, 6,741 were prescribed bupropion and 31,260 were prescribed varenicline. Examining baseline characteristics related to psychiatric history, it was generally balanced between varenicline and bupropion with slightly higher frequencies in the NRT group for previous antipsychotic or antidepressant use and previous psychiatric illness.

Ninety-two cases of suicide and non-fatal self harm were identified after 3 months of follow-up after the date of treatment initiation. For varenicline, Cox regression analysis showed no evidence of an increased risk of fatal and non-fatal self harm (HR=0.88, 0.52 to 1.49) or depression (HR= 0.75, 0.65 to 0.87) vs. NRT. For bupropion, a separate Cox regression analysis showed no evidence of an increased risk of fatal and non-fatal self harm (HR=0.83, 0.30 to 2.31) or depression (HR= 0.63, 0.46 to 0.87) vs. NRT. Similar findings were obtained for varenicline and bupropion using propensity score methods and instrumental variable analyses. There was no evidence that the association of smoking cessation products with suicide and self harm interacted with a history of psychiatric illness (P=0.57 for interaction).

Authors' Conclusions: There is no evidence of an increased risk of depression or suicidal behavior in users of varenicline or bupropion compared with NRT.

Strengths and Limitations: The authors mentioned several limitations associated with the study. This study was based on the recording of prescriptions in primary care but there was no information on over the counter medications used, which is most relevant to NRT. Repeat prescriptions and adherence were not assessed and there was no way of determining whether individuals actually used the drugs they were prescribed or when they started taking them. Another possible limitation was the influence of smoking abstinence on the primary outcomes. Varenicline has been shown to be more effective than the other products in achieving smoking abstinence in the short term. Therefore, the existence of a causal association between smoking abstinence and suicide or self harm may compromise the interpretation of the results. Next, a validated measure of depression was not used; instead initiation of antidepressant therapy was used as a proxy. In a previous CPRD study, about 80% of patients diagnosed with depression received an antidepressant prescription in their first year of diagnosis (though in the general population only a minority of patients with depression receive treatment). However, antidepressants are also used to treat anxiety and sleep disorders, thus antidepressant prescribing is not a pure measure of incident depression. Lastly, although the conventional regression showed a lower all cause mortality in patients prescribed varenicline compared with NRT, the authors believe that this association was likely caused by residual confounding, because this finding was not supported by the instrumental variable analysis. The instrumental variable analysis was conducted to provide unbiased estimates of the effects of treatments in the presence of residual confounding.

The authors discussed several strengths. First, data from the CPRD, one of the largest primary care databases in the world was used, which was amenable to the investigation of rarer outcomes. Secondly, the population of the CPRD is representative of the UK population. Thirdly, new CPRD linkages to ONS mortality statistics and HES (Hospital Episode Statistics) data resulted in better ascertainment of the suicide and self harm outcomes. Last, three different methods to assess the effect of confounding by indication, a major limitation of observational studies were used.

Study Summary for A Retrospective, Cohort Study Conducted by the Department of Veterans Affairs (VA) to Assess Mental Health Hospitalizations in Patients Who Received Varenicline or Nicotine Replacement Therapy

Below is an excerpt from a Safety Announcement posted on Oct 24, 2011 at: http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm#sa. A complete publication is not available.

The VA study was a retrospective cohort study to evaluate the incidence of mental health hospitalizations among veterans using varenicline or NRT. Patients starting varenicline or NRT between 1 May 2006 and 30 September 2007, but with no varenicline or NRT use in the previous year, were selected and matched in a 1:1 ratio to patients using NRT by use of propensity scores. The study's main outcome was psychiatric hospitalization 30 days after a prescription fill for varenicline or NRT.

The VA study population included 14,131 varenicline users and an equal number of NRT users. Among these patients, there were 16 psychiatric hospitalizations in varenicline-treated patients, and 21 in NRT patients. A Cox proportional hazards analysis showed no statistically significant difference in the risk of psychiatric hospitalization for varenicline users compared to NRT users (HR for varenicline /NRT = 0.76; 95% CI 0.40-1.46). A complementary analysis in a prevalent user cohort of patients who had used NRT in the past before initiating varenicline or refilling an NRT prescription also showed no statistically significant difference in psychiatric hospitalizations between the two treatment groups. Also, the results using time periods longer than 30 days after a prescription fill were similar.

An assessment of the power of the 4 studies to detect an increased risk of NPS events is provided in Appendix 6.2.

5.3.3.3. Observational Studies Summary and Conclusions

A review of the published literature identified 4 population-based observational studies that compared varenicline to another pharmacological smoking cessation treatment. They found no evidence that varenicline users were more likely to inflict fatal or non-fatal self-harm, to initiate pharmacological treatment for depression or to be hospitalized for a neuropsychiatric condition relative to users of NRT. Relative to bupropion users, varenicline users were no more likely to be treated at an emergency department or be hospitalized for a neuropsychiatric condition.

The results from these observational studies are consistent with the results from the clinical trials. These real-world data were gathered among a broader selection of patients, including patients with psychiatric disorders, and thereby generalize the clinical trials results to the overall population of smokers. Other strengths of these studies include their relatively large drug cohort sizes, the use of propensity scores to minimize the effects of potential confounders. The strengths also include that the authors conducted sensitivity analyses and analyses of secondary endpoints that increase confidence in the robustness of the findings. Like all observational studies, the lack of randomization in these studies leaves the potential for selection bias. Despite attempts to control for confounding, there is always the possibility of residual confounding. Two (Meyer et al and VA) of the 4 studies had limited power to detect a doubling of their primary endpoints. Two (pharmacological treatment for depression and hospitalization for an NPS condition) of the 3 endpoints were surrogates for the NPS events of interest.

5.4. Varenicline Neuropsychiatric Data Summary and Conclusions

As reviewed in this section, there has been an accumulation of varenicline NPS safety data over time, drawn from different sources that can be utilized in the evaluation of whether treatment with varenicline is causally associated with serious NPS events. These different data sources, which include nonclinical studies, postmarketing reports, large population-based observational studies, and randomized, controlled clinical trials represent different levels of the hierarchy of evidence, each with its own strengths and limitations.

In vitro and in vivo nonclinical studies including receptor selectivity studies and preclinical behavioral tests, provide no evidence of an association between varenicline and serious NPS adverse effects.

Postmarketing reports began to suggest an emerging signal for serious NPS events in September 2007, and continued through subsequent label changes. Reporting rates for NPS events subsequently declined to levels similar to those seen before the 2007 spike in reporting and remained relatively low and stable throughout 2013. Due to the limitations of postmarketing data these reports cannot establish a causal association between the events and varenicline.

At the time the boxed warning was implemented in 2009, 10 randomized, placebo-controlled Pfizer sponsored clinical studies had been completed. NPS AE data from these studies did not show evidence of an increased risk of NPS events with varenicline treatment compared to placebo. However, the small number of subjects with psychiatric co-morbidities, and the lack of use of validated psychiatric scales, rendered these data insufficient to verify or refute the postmarketing safety signal for serious NPS events.

In the 5 years since 2009, a substantial amount of data representing higher levels of the hierarchy of evidence have accumulated. This evidence includes 8 additional randomized, placebo-controlled studies (for a total of 18 such studies). Five of the studies included the C-SSRS and 2 of the studies specifically enrolled patients with psychiatric co-morbidities (MDD and schizophrenia/schizoaffective disorder), while a third focused on NPS symptoms during an enforced abstinence period. Both individually and analyzed collectively by meta-analyses, these 18 studies did not show evidence of an increased risk of NPS events in varenicline-treated subjects compared to placebo, other than events related to sleep disorders and disturbances. In addition to the studies conducted by Pfizer since 2009, multiple independent trials have now been published in the literature, and none of these trials found evidence of an increased risk for serious NPS events with varenicline.

Finally, the last 5 years have also seen the public release of the results of 4 large population-based observational studies. Consistent with the data from clinical trials, these real-world data which are based on a broad population of patients, including those with psychiatric disorders, do not show any increased risk for varenicline-treated patients compared to those treated with NRT or bupropion, with regards to any of the NPS endpoints studied. These observational study data therefore extend the validity of the clinical trial data to the general population of smokers.

6. VARENICLINE EFFICACY

Section 5.3 above showed that there is no evidence of an increased risk of serious NPS events with varenicline treatment as compared to other smoking cessation treatments, including placebo. The importance of maximizing access to varenicline is related to its superior efficacy compared to other treatments. This section provides a summary of the efficacy of varenicline.

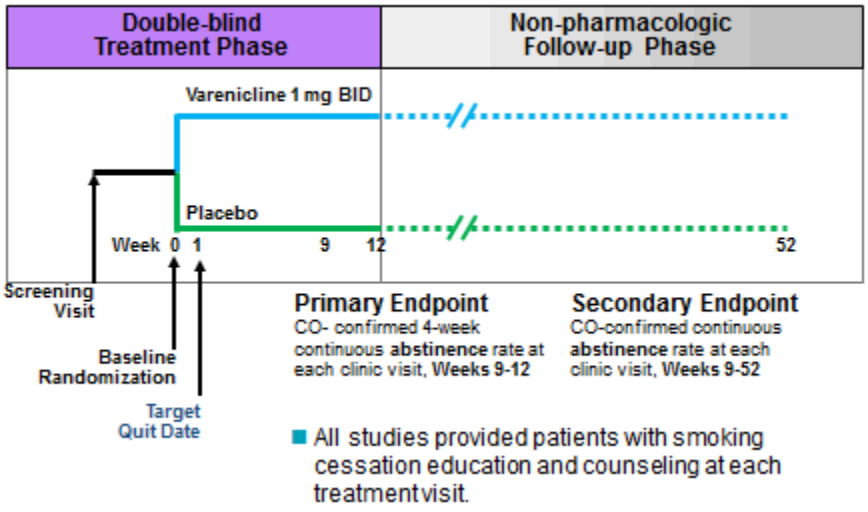
6.1. Overview of Efficacy Studies

As of the 25 February 2014 cut-off date for clinical trial data in this Briefing Document, a total of 18 randomized, placebo-controlled Pfizer-sponsored varenicline smoking cessation studies have been completed. Of these, ten Phase 3 and 4 studies were considered primarily efficacy studies. Key features of these 10 efficacy studies are summarized in Table 16 and in Appendix 1. Note that because the Schizophrenia Study (A3051072) was a safety/tolerability study and efficacy was not a primary endpoint (only 7-day point prevalence was collected), the efficacy data from this trial is not included in the discussion below.

Earlier varenicline studies included generally healthy subjects, while later studies included various populations of smokers. Some of the later studies focused on patients with a specific co-morbidity such as cardiovascular (CV) disease, chronic obstructive pulmonary disease (COPD), and MDD. Other efficacy studies looked at populations in countries outside the US, one evaluated using a flexible quit date chosen by the patient rather than a fixed quit date of 1 week after starting treatment and another focused on subjects who had previously taken varenicline and either failed to quit or had relapsed.

All 10 studies consisted of 12 weeks of active treatment and either 12 weeks (4 studies) or 40 weeks (6 studies) of non-treatment follow-up, with a primary efficacy measure of CO-confirmed continuous abstinence (CA) from Weeks 9 to 12 and a secondary efficacy measure of CO-confirmed CA from Weeks 9 to 24 or 9 to 52. This general study design is shown Figure 19 below:

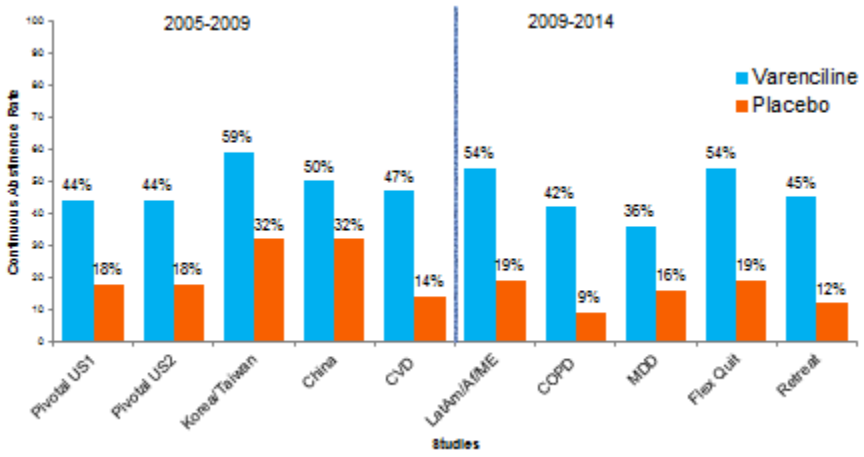
Figure 19. Basic Study Design for Placebo-Controlled Varenicline Phase 3 and 4 Efficacy Studies



6.2. Primary Efficacy Endpoint Results

Results of the primary efficacy endpoint of CA Week 9-12 are presented below in Figure 20 and Table 14.

Figure 20. Week 9-12 Continuous Abstinence Rates in Completed Placebo-Controlled Phase 3 and 4 Varenicline Studies



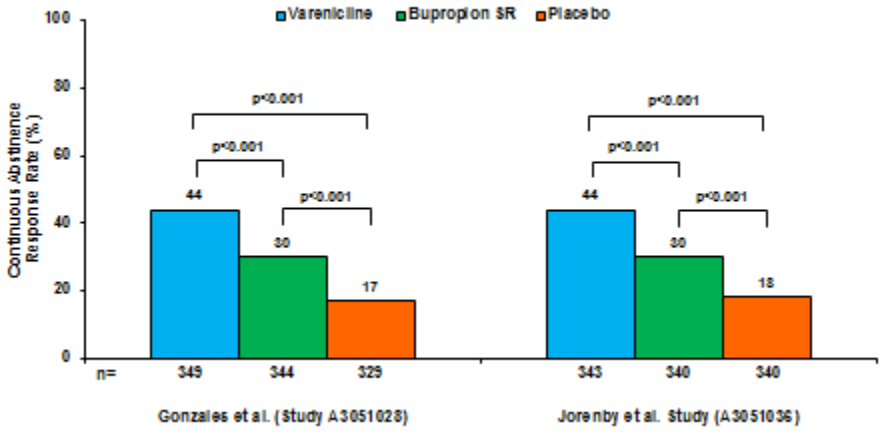
Week 9-12 CA rates ranged from 36% to 60% in varenicline subjects and 9% to 32% in placebo subjects. In each of the 10 efficacy studies, the difference in CA rates between varenicline and placebo was statistically significant. Table 14 lists the CA rates, ORs, and p-values for the 10 efficacy studies.

Table 14. Week 9-12 Continuous Abstinence Rates and Odds Ratios in Completed Placebo-Controlled Phase 3 and 4 Varenicline Efficacy Studies

Study	Varenicline n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI) vs placebo	p-value
Pivotal Study	155/349 (44.4)	61/344 (17.7)	3.91 (2.74, 5.59)	<0.0001
Pivotal Study	151/343 (44)	60/340 (17.7)	3.85 (2.69, 5.50)	<0.0001
Taiwan/Korea Study	75/126 (59.5)	40/124(32.3)	3.22 (1.89, 5.47)	<0.0001
Multinational Asian Study	83/165 (50.3)	53/168 (31.6)	2.31 (1.45, 3.67)	0.0003
Multinational Study LatAm/Af/MEast	209/390 (53.6)	37/198 (18.7)	5.76 (3.74, 8.88)	<0.0001
CV Study	167/353 (47.3)	50/350 (14.3)	6.05 (4.13, 8.86)	<0.0001
COPD Study	105/248 (42.3)	22/251 (8.8)	8.40 (4.99, 14.14)	<0.0001
Depression Study	92/256 (35.9)	42/269 (15.6)	3.35 (2.16, 5.21)	<0.0001
Flexible Quit Study	262/486 (53.9)	32/165 (19.4)	6.03 (3.80,9.56)	<0.0001
Re-treatment Study	112/249 (45.0)	29/245 (11.8)	7.08 (4.34, 11.55)	<0.0001

The two Phase 3 pivotal studies included an active comparator arm, bupropion (Zyban®), in addition to placebo. As shown in Figure 21, in both these studies, varenicline subjects had statistically higher Week 9-12 CA rates compared to bupropion, as well as compared to placebo (for all comparisons p<0.001).

Figure 21. Week 9-12 Continuous Abstinence Rates in Phase 3 Pivotal Studies: A3051028 and A3051036

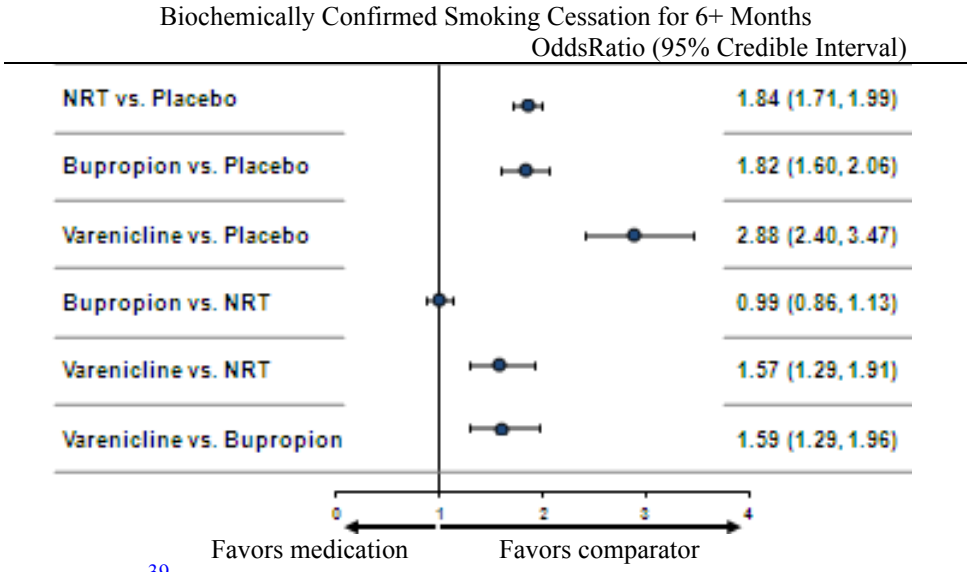


6.3. Cochrane Efficacy Meta-Analysis

A network meta-analysis of the comparative efficacy of varenicline, NRT, bupropion, other pharmacotherapies and placebo as aids for smoking cessation was conducted and published by the Cochrane Group[39]. A network meta-analysis is a statistical technique in which both direct (head-to-head randomized controlled trials) and indirect evidence can be examined, which increases the power and interpretability of a comparative analysis.[55]

The meta-analysis included a total of 267 studies and 101,804 study participants. A total of 117 NRT studies, 49 bupropion studies, and 14 varenicline studies were included in the main analysis. The primary outcome was sustained smoking of at least 6 months from the start of treatment. Biochemically confirmed abstinence (on the basis of expiratory CO, cotinine in plasma, urine or saliva, or plasma thiocyanate) was favored over self reports. Figure 22 shows a forest plot of the ORs for the comparisons between varenicline, bupropion, and NRT, the first line pharmacotherapies for smoking cessation, and placebo.

Figure 22. Cochrane Group Network Meta-Analysis of the Comparative Efficacy of Varenicline, NRT, Bupropion, and Placebo.



Cahill et al. [39]

As calculated in the meta-analysis, the OR for varenicline vs placebo was 2.88 (95% Credible Interval [CredI]: 2.40, 3.47), for varenicline vs single forms of NRT 1.57 (95% CredI: 1.29, 1.91), and varenicline vs bupropion 1.59 (95% CredI: 1.29, 1.96).

6.4. Efficacy Summary and Conclusions

Across the Pfizer clinical development Phase 3-4 program, including studies in different regions of the world, in smokers with co-morbid conditions, including psychiatric conditions, in smokers using a flexible quit date approach, and in smokers being re-treated with varenicline, varenicline has consistently shown statistically significantly higher CA rates than placebo. In studies that included an active comparator, varenicline showed statistically significantly higher CA rates than bupropion at Weeks 9-12. The Cochrane network meta-analysis that compared efficacy among the 3 currently approved smoking cessation products at 6 months after treatment start, showed that varenicline is significantly more effective than other approved monotherapies.

7. PUBLIC HEALTH IMPACT OF TOBACCO AND URGENCY OF CHANTIX LABEL CHANGES

Considering the varenicline safety and efficacy data presented above, this section describes the public health burden caused by smoking, the challenges of smoking cessation, and an illustration of the contribution of varenicline in addressing this public health problem.

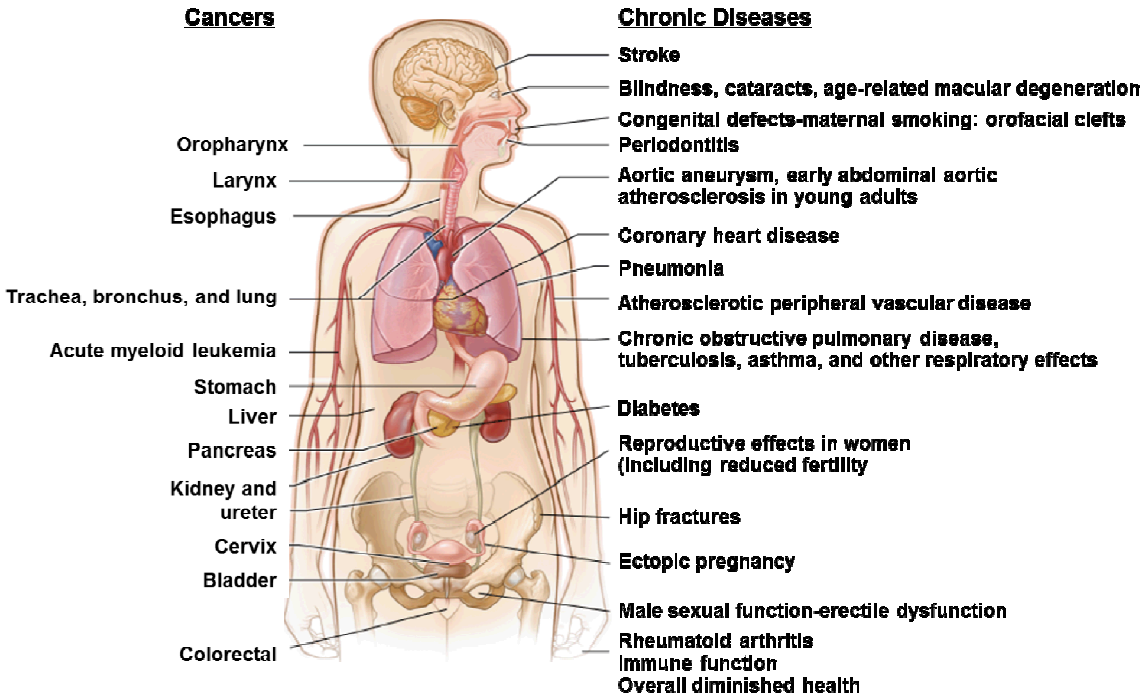
7.1. Harm from Smoking

The effects of smoking on mortality and morbidity remain striking and incontrovertible. With regards to mortality, current statistics include:

- Cigarette smoking is the number one preventable cause of death in the US[56], responsible for more than 480,000 deaths each year in this country. This is about 1 in 5 deaths[56,20,57] and it is more than the deaths from human immunodeficiency virus (HIV), illegal drug use, alcohol use, motor vehicle injuries, and firearm-related incidents combined. [58]
- Smoking causes about 90% of all lung cancer deaths in men and women.[59] More women die from lung cancer each year than from breast cancer.[6]
- About 80% of all deaths from COPD are caused by smoking. [59]

With regard to morbidity, cigarette smoking has been causally linked to diseases of nearly all organs of the body and to diminished health status, as shown in Figure 23.[20] Indeed, diseases caused by smoking continue to be newly identified despite 50 years of research, including such common diseases as diabetes mellitus, rheumatoid arthritis, and colorectal cancer.[20]

Figure 23. Health Consequences Causally Linked to Smoking, 2014 Report of the Surgeon General



Surgeon General Report 2014[20]

The morbidity caused by cigarette smoking has a significant impact on healthcare costs. Smoking-related health care expenditures account for an estimated 5%–14% of the total health care expenditures in the US. The results of a model-based study from Rumberger et al suggest that in the US, the annual costs to the economy attributable to smoking were in excess of $298 billion, including workplace productivity losses of approximately $67.5

billion, premature death losses of $117 billion, and direct medical expenditures of $116 billion.[60]

7.2. Health Benefits from Smoking Cessation

Quitting smoking has both short and long term health benefits. In the first 24 to 48 hours after cessation, blood pressure and heart rate may drop and blood levels of CO return to normal. In the first weeks and months after quitting, circulation may improve and lung function can increase. After 1 year, the excess risk for coronary heart disease is reduced by half compared with that of a smoker. By 10 years, the risk of lung cancer death is half that of a smoker, and by 15 years, stroke risk has returned to that of a non-smoker. [61]

Life expectancy is shortened by more than 10 years among current smokers, as compared with those who had never smoked. Cessation at any age has considerable benefit, with a greater impact in smokers who quit at younger ages. Adults who had quit smoking at 25 to 34, 35 to 44, or 45 to 54 years of age gained about 10, 9, and 6 years of life, respectively, as compared with current smokers.[62]

Smoking prevalence rates have dropped from 21% to 18% within the last ten years[5]. While there has been progress, we are still far from achieving the *Healthy People 2020* objective of reducing the proportion of US adults who smoke cigarettes to ≤12%. Appropriate utilization of any of the approved smoking cessation treatments, including varenicline, may help reach this goal.

7.3. Challenges of Smoking Cessation

Regardless of the available treatment options, more than half (52.1%)[63] of quit attempts by US smokers are unaided attempts with an average success rate as low as 5%[64]. NRT utilization is facilitated by over-the-counter (OTC) availability. Despite ease of access, the impact of NRT therapy, particularly when obtained OTC, has been limited.[65] Published literature shows that at least 38% of US smokers have tried NRT and failed [66] Having efficacious options for smokers who previously failed on NRT is essential for increasing their likelihood of successful cessation.

As was noted in Section 6.3, a recent Cochrane review concluded that varenicline is significantly more effective than other approved monotherapies, specifically including nicotine patch (OR 1.51; 95% CredI 1.22 to 1.87), nicotine gum (OR 1.72; 95% CredI 1.38 to 2.13), 'other' NRT (inhaler, spray, tablets, lozenges; OR 1.42; 95% CredI 1.12 to 1.79), and bupropion (OR 1.59; 95% CredI 1.29 to 1.96).[39]

However, although varenicline has been shown in the Cochrane review to be more efficacious than other approved monotherapies, it cannot be excluded that its use may be hindered by physicians' and patients' lack of understanding regarding the specifics and intent of the boxed warning. Indeed, quantitative market research data show that 54% of patients who are recommended CHANTIX by their physician refuse the prescription due primarily to concerns about adverse events. The same research indicates that nearly one-third of all CHANTIX requests made by smokers are not granted by the physician, due primarily to

concerns about adverse events; the physician denial rate jumps to 44% when the CHANTIX request is made by a smoker with psychiatric co-morbidities.[67]

If the boxed warning in the CHANTIX label inaccurately conveys the currently available data regarding the risk of serious NPS events with varenicline use and thereby results in under-utilization of the product, increased morbidity and mortality from continued smoking could result.

7.4. BENESCO Model Showing Estimates of the Impact of Varenicline Treatment on Reduction in Morbidity and Mortality from Smoking-Related Diseases

The Benefits of Smoking Cessation on Outcomes (BENESCO) model, is a Markov model that simulates the health outcomes and costs of a hypothetical cohort of adult smokers who make a single attempt to quit smoking with either varenicline, NRT, bupropion or unaided.[68] Successful cessation has the potential, over time, to reverse or prevent the co-morbidities associated with smoking and the mortality from smoking-related disease. Modeling can simulate the impact on morbidity and mortality of different smoking cessation interventions used in a population over time.

The BENESCO model accounts for the epidemiological pattern and chronicity of the following smoking-related diseases: COPD, lung cancer, coronary heart disease (CHD), and stroke. This model assumes that 25% of US smokers make a single attempt to quit in the first one-year cycle of the simulation. Additionally, the entire cohort is assumed to use the same intervention for the attempt. Subjects are then classified into smokers or quitters throughout the duration of the model. Estimated quit rates at 1 year that are used in the model are 22.4% for varenicline, 15.4% for bupropion, 15.4% for NRT, and 5% for unaided cessation, based on published clinical trial data (varenicline, bupropion), indirect comparison (NRT), and published literature (unaided cessation). Subsequently, the relapse rate per year was assumed to be equivalent across treatments and was 6.3% for years 2 through 5, 2% for years 6 through 10, and 1% for year 11 and after. The resulting morbidity and mortality estimates are then compared between the interventions.[68]

There are limitations to be noted. The impact of adherence to initial smoking cessation medication and associated effect on quitting is not explicitly modelled. Additionally, only 4 smoking related diseases are included and disease events are assumed to be mutually exclusive, meaning a subject cannot simultaneously have 2 co-morbidities occurring in the same year. Next, a restricted hierarchy exists whereby subjects can enter the CHD or stroke health state and subsequently transition to the COPD or lung cancer state, but once a subject transitions into COPD or lung cancer they reside there until death, due to the irreversible nature of these conditions. Lastly, no smoking related events are assumed to occur before age 35, as the 4 smoking-related morbidities examined are uncommon before this age. The effect of these last 3 limitations results in modelled outcomes which may underestimate the true impact of smoking cessation.[68]

7.4.1. BENESCO Results

In the BENESCO publication by Howard et al., the model assumes that 11,925,455 smokers in the US (25% of the US adult smoking population in 2004) made an attempt to quit.[68]

The outcomes derived from the published BENESCO model show that one-time treatment with varenicline would prevent the largest number of smoking-related deaths and co-morbidity in this population. When a less efficacious method is used, excess smoking-related morbidity and mortality is estimated to result. For example, as shown in Table 15, excess smoking-related mortality is estimated to be between approximately 388 and 964 deaths within 2 years from the attempt and between approximately 58,000 and 144,000 deaths using a lifetime view, if all smokers who make a quit attempt in 1 year used a smoking cessation method with a lower quit rate than varenicline. Similarly, smoking-related morbidity ranges from 1,873 to 4,653 cases within 2 years following quit attempt and approximately 104,000 to 259,000 over the lifetime when a less-efficacious method is used.[68]

Table 15. BENESCO Estimates of Excess Smoking-Related Mortality and Morbidity with Comparator vs Varenicline

	Cohort of smokers making quit attempt in Howard et al.[68] (N=11,925,455)	
	2-year	**Lifetime**
Excess Smoking-related Mortality		
Unaided vs Varenicline	964	143,966
Bupropion vs Varenicline	388	57,917
NRT vs Varenicline	390	58,248
Excess Smoking-related Morbidity		
Unaided vs Varenicline	4,653	258,708
Bupropion vs Varenicline	1,873	104,079
NRT vs Varenicline	1,883	104,673

Smoking-related conditions include Chronic Obstructive Pulmonary Disease, Lung Cancer, Coronary Heart Disease, Stroke.

7.5. Public Health and BENESCO Summary and Conclusions

The health consequences of smoking can affect multiple organ systems and are related to many diseases. The most common of these are various cancers, cardiovascular disease, stroke, and COPD. The health benefits of quitting smoking, however, can begin almost immediately with drops in blood pressure, heart rate and CO levels, and these benefits continue to accrue until, by 15 years after quitting, some parameters, such as stroke risk, are similar to non-smokers. The BENESCO model is one method that can be used to translate

these physiologic benefits into quantifiable effects on reductions in morbidity and mortality due to some of the most clinically significant smoking-related conditions. Despite increased public health awareness of the dangers of smoking and available treatments, the majority of smokers do not utilize a smoking cessation aid. Among those who do make an attempt to quit using a smoking cessation aid, the BENESCO model demonstrates that utilization of an agent with greater efficacy not only can confer substantial benefits to an individual patient but also can reduce the overall public health burden due to smoking-related morbidity and mortality. Given the significant implications in terms of life lost and health care costs of tobacco-related morbidity and mortality, a delay in abstinence can have significant consequences.

8. OVERALL SUMMARY AND CONCLUSIONS

Varenicline was developed specifically as a partial agonist targeting the receptors associated with nicotine's addictive properties. Its receptor pharmacology demonstrates lack of relevant interaction with neurotransmitter systems associated with psychiatric adverse events and there was no evidence of a risk of neuropsychiatric events from either preclinical or clinical studies. However, following the emergence of postmarketing reports describing neuropsychiatric events in smokers taking CHANTIX, warnings were added to the product label, ultimately resulting in a boxed warning in 2009.

Since 2009, 8 additional randomized, controlled clinical trials have been conducted. Five of these studies utilized the Columbia Suicide Severity Rating Scale, a validated instrument designed to prospectively assess suicidal ideation and behavior. Additionally, 2 of the studies were conducted in patients with psychiatric co-morbidities, major depressive disorder in one and schizophrenia/schizoaffective disorder in the other. Neither of these 2 studies showed an increase in neuropsychiatric symptoms as measured by validated psychiatric scales with varenicline treatment compared to placebo. Furthermore, a meta-analysis of the 18 randomized, placebo-controlled varenicline studies also showed no evidence of increased risk of NPS events, other than sleep disorders, for varenicline compared to placebo.

Four large, independently conducted population-based observational studies have been publically reported. These studies included patients from the US Military Health System[52] and US Veterans Health Administration[51], and patients within UK general practices[50] and Danish national registries[54]. These observational studies, using different NPS endpoints, and including smokers with and without psychiatric history, consistently demonstrated a lack of increased risk of NPS event with varenicline treatment compared to either NRT or bupropion. Importantly, these findings provide evidence of external validity of the randomized clinical trials -they show that the results of these trials are generalizable to the overall population of smokers.

Although postmarketing pharmacovigilance is an important component of drug safety surveillance, it is usually not possible to attribute causality based solely on postmarketing reports. The hierarchy of evidence, and the concordance of results from the randomized clinical trials and population-based observational studies, do not confirm the signal identified from varenicline postmarketing reports of serious NPS events and do not support a causal

association between varenicline usage and serious NPS events. The totality of the currently available evidence is, therefore, inconsistent with a boxed warning.

Timely communication of the current evidence within the CHANTIX label will enable the patient and prescriber to make an informed decision about treatment. Used appropriately, a boxed warning can help to ensure that serious adverse reactions associated with that product are properly considered in that treatment decision. However, a boxed warning that discourages utilization of the most effective treatment option can, in this setting, have implications for tobacco-related morbidity and mortality, and should meet appropriate standards of evidence.

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APPENDICES

Appendix 1. Description of Varenicline Phase 3 and 4 Efficacy Studies

Table 16. Summary of Phase 3 and 4 Randomized, Placebo-Controlled, Double-Blind Varenicline Efficacy Studies

Objective Study Number	Duration	Treatment Groups	Number of Subjects[a]
Pivotal Study 1 **A3051028**[69]	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	349 329 344 Total: 1022
Pivotal Study 2 **A3051036**[70]	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	343 340 340 Total: 1023
Study in Taiwan and Korea **A3051045**.[71]	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	126 124 Total: 250
Multinational Asian Study **A3051055**.[72]	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	165 168 Total: 333
CV Disease Study **A3051049**.[73]	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	353 350 Total: 703
COPD Study **A3051054**[74]	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	248 251 Total: 499
Multinational Study: **Africa, Mid-East, S America** **A3051080**[75]	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	390 198 Total: 588
Flexible Quit Date Study **A3051095**[76]	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	486 165 Total: 651
Depression Study **A3051122**[77]	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	256 269 Total: 525
Re-treatment Study **A3051139**[78]	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	249 245 Total: 494

BID=wice a day; QD=once a day.
a. No. of Subjects = subjects randomized and treated by treatment group and in total

Appendix 2. MedDRA Preferred Terms Contained in Neuropsychiatric-Related SMQs

The following SMQs were used in the analyses of postmarketing data and/or clinical trial data. The list below reflects MedDRA version 16.0.

The **Suicide/Self-injury SMQ** [narrow] includes the following PTs: Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Poisoning deliberate, Self injurious behavior, Self-injurious ideation, Suicidal behavior, Suicidal ideation, and Suicide attempt. The suicidal ideation subset of the SMQ included the PTs Depression suicidal, Self-injurious ideation, and Suicidal ideation. The suicidal/self-injurious behavior subset included the PTs Completed suicide, Intentional overdose, Intentional self-injury, Poisoning deliberate, Self-injurious behaviour, Suicidal behaviour, and Suicide attempt.

The **Hostility/Aggression SMQ** [narrow] includes the following PTs: Aggression, Amygdalotomy, Anger, Antisocial behaviour, Antisocial personality disorder, Belligerence, Borderline personality disorder, Child abuse, Conduct disorder, Homicidal ideation, Homicide, Hostility, Incest, Intermittent explosive disorder, Physical abuse, Physical assault, Psychopathic personality, Sexual abuse, and Violence-related symptom.

Appendix 3. Nonclinical Data

Appendix 3.1. Nonclinical Data Through 2009

In addition to a comprehensive pharmacology, pharmacokinetic, and toxicology program conducted to support registration, the pharmacology of varenicline was further characterized via its in vitro receptor selectivity and in vivo effects on neurotransmitter release, as well as with animal tests that are routinely used in the evaluation of potential adverse NPS effects.

Selectivity for α4β2 nAChRs

Varenicline is highly selective for α4β2 neuronal nAChRs with substantially lower binding affinities for other nAChRs and at least 850-fold lower affinity for other ion channels, transmitter receptors, transporters and enzymes (Table 17).

These data show that at therapeutic unbound brain concentrations, varenicline does not bind to targets that have been implicated in serious NPS events, in particular dopaminergic, serotonergic, adrenergic, GABA-ergic, glutamatergic, neurokinin and cannabinoid receptors or transporters, or the enzyme monoamine oxidase-A (MAO-A).

Table 17. In Vitro Affinities and Inhibitory Potencies of Varenicline

Nicotinic nAChR subtypes[a]		**Transmitter receptors[a]**	
α4β2	0.4	Dopaminergic	>1,000
α3β4	86	Alpha-Adrenergic	>10,000
α6/α4β2	111	Beta-Adrenergic	>10,000
α7	125	Serotonergic	>1,000
α1β1γδ	8,200	Histaminergic	>1,000
		GABA-ergic	>1,000
Ion Channels[a]		Glutamatergic	>1,000
Calcium	>1,000	Cannabinoid	>1,000
Sodium	>1,000	Muscarinic	>10,000
Potassium	>1,000	Opioid	>1,000
$GABA_{Cl}$	>1,000	Neurokinin	>1,000
HERG	>10,000		
Serotonin ($5\text{-}HT_3$)	350	**Transporters[a]**	
		Dopamine	>1,000
Enzymes[a]		Noerepinephrine	>1,000
MAO-A	>1,000	Serotonin	>1,000
Protein Kinase	>1,000	Gamma-aminobutyric	>1,000
Cytochrome P450	>1,000	Glutamate	>1,000
		Choline	>1,000

hERG = human ether-à-go-go related gene.
a. Binding affinities (Ki) or inhibitory concentrations (IC50) in nM of varenicline. Values >1,000 or >10,000 indicate no significant inhibition of radioligand binding at a test concentration of 1 or 10 μM varenicline.
Data from Rollema et al 2007[79], 2010[24], 2014[80]

Effects on Neurotransmitter Release

Varenicline's effects on neurotransmitter release as measured by microdialysis in the brain from freely moving rats, are consistent with its binding affinities for receptors and transporters that regulate transmitter release. Low doses of varenicline (0.03-1 mg/kg via oral gavage increase mesolimbic dopamine release in rat nucleus accumbens via its interaction with α4β2 containing nAChRs; this mechanism underlies its efficacy as a smoking cessation aid.[79] In contrast, microdialysis studies in rat prefrontal cortex show that at pharmacologically-relevant doses (<1 mg/kg subcutaneous [SC]), varenicline does not significantly modulate the release of cortical neurotransmitters, such as dopamine, norepinephrine, serotonin and ACh, which are thought to play important roles in mediating processes that are impaired in many neuropsychiatric disorders, and only increases the release of histamine.[81]

These results indicate that it is unlikely that varenicline administration would result in cortically-mediated NPS AEs that are associated with increases or depletions of key cortical neurotransmitters.

Animal Behavioral Tests

The potential for varenicline to induce neurological and/or behavioral effects in animals was assessed as part of the nonclinical development program.[82] The neurological effects of varenicline were evaluated in a safety pharmacology study in mice dosed once with varenicline by oral gavage at doses from 0.32 to 100 mg/kg. A variety of neurological and behavioral changes were described in animals given 32 or 100 mg/kg varenicline. At a lower dose, 10 mg/kg, mice exhibited neurological signs (mild, transient tremors) shortly after dosing, but appeared normal at the 1 and 2 hour post-dose time points. No neurological or behavioral effects were described in animals receiving doses <10 mg/kg. In a 9-month repeat-dose toxicity study with a 5-week recovery period in cynomolgus monkeys, a behavioral assessment was included for animals in the control and 0.4 mg/kg/day dose groups. Behavior was assessed for the last 5 days of treatment through Recovery Day 5, and no adverse effects were observed. In an oral pre- and postnatal development study, varenicline was administered to pregnant rats from Gestation Day 6 to Lactation Day 20 at doses of 0, 0.3. 3, or 15 mg/kg. An assessment of auditory startle response (ASR) conducted on the F1 generation on post-natal day 80-87 showed an increase in the maximum amplitude of the ASR in males at 15 mg/kg, although there was no effect on the mean amplitude of the ASR. There were no behavioral effects on F1-generation female rats at 15 mg/kg, nor were there any effects on ASR at ≤3 mg/kg. Taken together, these data do not suggest the potential for varenicline to produce behavioral effects in animals at human therapeutically relevant exposures.

Varenicline has also been examined in a variety of animal behavioral tests commonly used to evaluate whether compounds affect NPS function.

A Forced Swim Test (FST, also referred to as a behavioral despair test) was used as a test of mood (depression and anhedonia). Animals placed in an enclosed container filled with water

were scored for active (swimming and climbing) or passive (immobility) behavior. The duration of immobility time is thought to reflect 'negative mood' or 'despair', and drug-induced decreases in immobility time are interpreted as antidepressant-like activity. Pretreatment with all classical antidepressants decreases immobility time compared to vehicle-treated animals[83], while certain drugs known to cause NPS events in patients increase immobility time and show 'pro-depressant-like' activity in the FST[84,85]. Varenicline (0.2-5.6 mg/kg SC) was found to decrease immobility time, similar to classical antidepressants in this test.[86]

Tests to evaluate information processing and cognitive function included sensory gating tests, which measure the ability of the brain to filter out irrelevant stimuli and focus attention to relevant environmental stimuli. Varenicline was evaluated in three sensory gating tests, the acoustic startle response (ASR), prepulse inhibition (PPI) and auditory gating.[81] In the mouse ASR test, in which a drug-induced excessive reflexive response (startle amplitude) to an external loud noise is thought to indicate increased reactivity, arousal and irritability, varenicline (0.1-3.2 mg/kg SC) and nicotine (0.32-3.2 mg/kg SC) caused non-significant increases in the startle amplitude compared to controls, except for a marginal, statistically-significant increase after 1 mg/kg of varenicline. The antipsychotic risperidone significantly decreased the startle amplitude. In the mouse PPI test, which measures the suppression of the amplitude of the ASR that occurs when the startling stimulus is immediately preceded by a weak sensory pre-stimulus (prepulse), varenicline (0.1 – 3.2 mg/kg SC) caused an increase in PPI (statistically significant only at 1 mg/kg), while risperidone caused a relatively larger increase in PPI that is typical for antipsychotics. Finally, the effects of varenicline on auditory gating were studied in anesthetized rats. Unlike amphetamine, which disrupts auditory gating, administration of varenicline (1 mg/kg, intravenous) did not influence physiological auditory gating in hippocampus and entorhinal cortex. The same dose of varenicline significantly reversed the amphetamine-induced gating deficit in rat hippocampus.

Varenicline was studied in several tests to address different domains of cognitive functions. Varenicline did not impair performance in any of the these tests, including effects on nicotine withdrawal-associated deficits in a contextual fear conditioning paradigm, a measure of learning and memory[87], in the novel object recognition test, a test of episodic memory, on the sustained attention task with distractor, a test of attentional control, and in a spontaneous theta oscillations model, a test of information processing[81].

Appendix 3.2. Current Nonclinical Data

Several animal behavioral tests that have relevance for NPS events and varenicline treatment have been published since 2009 and are briefly summarized here.

Antidepressant and Anxiolytic Tests

Additional FST data confirmed that varenicline (0.1-3 mg/kg intraperitoneally [IP]) does not prolong immobility over a range of doses that include exposures exceeding therapeutic concentrations in patients on 1 mg BID varenicline.[88,89,90] In contrast, cyclosporine, a drug

that causes NPS AEs in patients, was recently reported to have 'pro-depressant-like' activity in the FST.[91]

A recent study reported that varenicline reduced the dysphoric-like state associated with nicotine-withdrawal, using intracranial self-stimulation to measure brain reward function in rats.[92] Varenicline was also examined in animal tests that are used to assess the anxiolytic or anxiogenic effects of compounds. After acute (0.01-1 mg/kg IP) and repeated administration (1.8 mg/kg/day SC), varenicline shows anxiolytic-like activity in the marble-burying test, a type of 'defensive' burying behavior by mice that is reduced by anxiolytics and antidepressants.[89,90] In the novelty-induced hypophagia test, which measures the effect of drugs on reduced food intake in response to a novel unfamiliar environment, varenicline also exhibited anxiolytic-like activity after acute administration (0.1 mg/kg IP), but had no effect after repeated (1.8 mg/kg/day SC) administration.[89] In the Elevated Plus Maze test that can be used to study anxiolytic effects of drugs, varenicline (0.5 and 1 mg/kg ip), which had no effect by itself, attenuated the scopolamine-induced impairment, and also reduced the memory improvement induced by nicotine.[93] Finally, in an Elevated Zero Maze test, varenicline (0.1-1 mg/kg IP) had no anxiogenic effect.[89]

Recent sensory gating data on varenicline are in good agreement with previously published data, in that therapeutic concentrations do not cause impairment of auditory gating in several paradigms. Varenicline (1.2 mg/kg SC) improves performance in a mouse paired-click task[94] and at 0.3-6 mg/kg IP restores gating in mice with a genetic auditory gating deficit[95]. In addition, varenicline (0.5-3 mg/kg SC) had no effect on the amplitude of the startle response in the ASR test[96] and did not change PPI in naive animals, but caused a small increase in PPI at 1 mg/kg in high-inhibitory animals, similar to that observed following nicotine[96]. Taken together, the results of these tests demonstrate that a wide range of doses, varenicline does not impair sensory gating in laboratory animals.

Varenicline has been studied in 2 additional animal memory and learning tests. In the Morris Water Maze, a test that is used to examine effects on spatial learning and memory, varenicline (0.04-1 mg/kg SC) improved performance times on the first day, but not on Days 2 and 3.[97] In the 5-Choice Serial Reaction Time Task that measures effects on attention and impulsivity, varenicline (0.5-2.5 mg/kg IP), increased premature responding at low doses, without affecting other behavioral parameters[98], similar to the effects of nicotine (0.1-1 mg/kg SC) in this test[99].

Nonclinical Conclusions

The results of in vitro studies demonstrate that varenicline has high selectivity for the α4β2 subtype of nAChRs and does not bind to targets that have been implicated in serious NPS adverse effects. The results of the in vivo tests demonstrate that varenicline neither increases nor depletes levels of key cortical neurotransmitters and does not impair behavior in several animal tests that assess effects on mood and cognitive processing. The combined results of nonclinical studies do not provide evidence for an association between varenicline and serious NPS adverse effects.

Appendix 4. Postmarketing Data

Appendix 4.1. Overview of Postmarketing Data

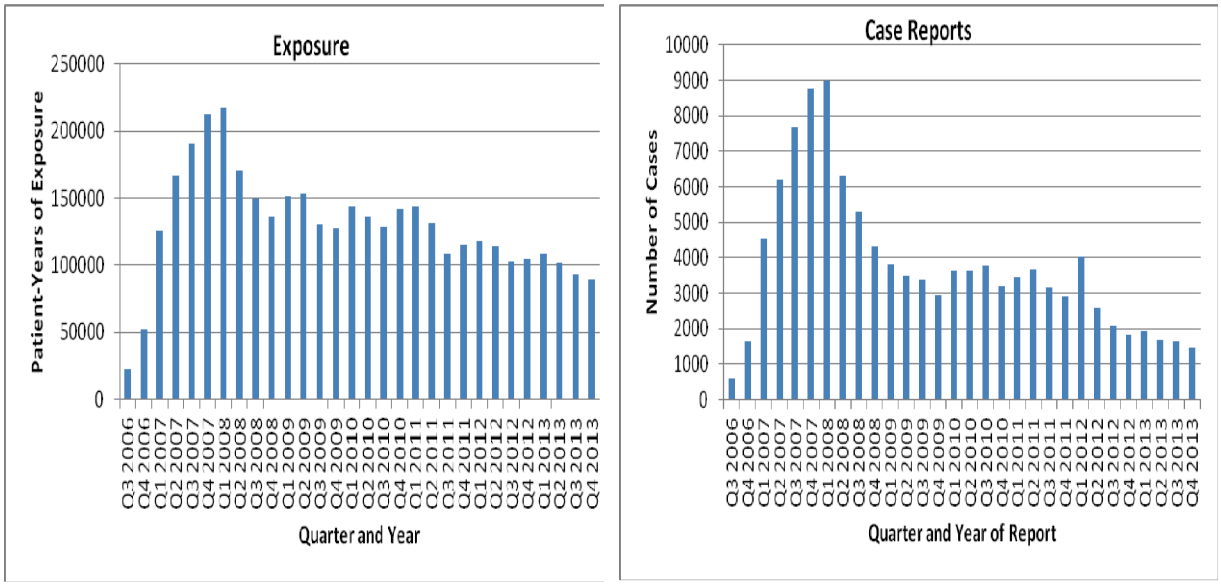
Postmarketing surveillance, based on spontaneous reports, is a valuable tool for monitoring a drug's safety post-approval. Postmarketing surveillance enables the early detection of potential safety signals not discovered during pre-marketing clinical trials, including rare/idiosyncratic events that may not be amenable to detection in more robust datasets such as clinical trials or observational studies.

However, spontaneous postmarketing reports have significant limitations that are important to consider when interpreting the data. These include:

- Reports are voluntary and unsolicited and therefore, there is the potential for under-reporting, as well as duplication of reporting.
- A variety of factors may bias reporting including length of time a product has been on the market ("Weber effect"[100]), patient exposure, geographical reporting environment, detailing time, media coverage, regulatory actions, and labeling changes.
- The exact number of patients utilizing the product is not usually available, so exposure can only be estimated and an incidence rate cannot be determined.
- Report quality is often insufficient to allow meaningful case assessment. Key information such as when/how long the medication was taken, time to onset of the event, reversal with medication termination, patient medical history, concomitant medications, and, important for varenicline, smoking status is often missing, despite multiple attempts to obtain follow-up information.
- Cannot estabalish causality, in particular when the AEs of interest occur with high frequency as background in the population.

Pfizer began to receive postmarketing reports for CHANTIX in 3rd quarter 2006, after market introduction. As with all newly marketed products, the number of cases reported increased as market utilization increased. This can be seen in Figure 24, which shows exposure and the number of cases reported by year and quarter through 4th quarter 2013.

Figure 24. Estimates of Postmarketing Exposure to Varenicline and the Number of Case Reports Received through 4th Quarter 2013



The left-hand panel in Figure 24 shows estimated patient exposure, calculated as patient-years. These data are derived from prescription data provided by an independent source, IMS Health and are calculated with the assumption that the standard dose is 2 tablets per day. The right-hand panel in Figure 24 shows the number of case reports received for varenicline and entered into the Pfizer safety database, a central repository for postmarketing cases for all Pfizer products. As can be seen, exposure and overall case reporting peaked in 1st quarter 2008, followed by a decline in both measures. The cumulative estimated exposure to varenicline through 4th quarter 2013 was 3,891,536 patient-years. The cumulative number of varenicline postmarketing case reports for the same period was 112,690.

Appendix 5. Meta-Analysis of NPS Clinical Trial Data through 2009

A total of 10 randomized, placebo-controlled Pfizer-sponsored varenicline clinical trials were completed by 2009. These studies provided data for 3,091 subjects treated with varenicline and 2,005 subjects treated with placebo. Subjects with active psychiatric disorders were excluded from the 10 trials based on predetermined inclusion/exclusion criteria. Table 18 summarizes these studies and the following sections describe the meta-analysis of these studies.

Table 18. Randomized, Placebo-Controlled, Double-Blind Varenicline Studies Completed as of 2009 and Contributing NPS Safety Data

Study Objective Study Number	Duration	Treatment Groups	Number of Subjects[a]
Dose-ranging study **A3051002**	Varenicline: 6 weeks treatment plus 1 week placebo; Zyban: 7 weeks treatment nontreatment follow-up to Week 52	Varenicline 0.3 mg QD Varenicline 1 mg QD Varenicline 1 mg BID Zyban 150 mg BID Placebo	126 126 125 126 123 Total: 626
Titration Study **A3051007** **(nontreatment follow-up in Study A3051018)**	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline 0.5 mg NT Varenicline 0.5 mg T Varenicline 1 mg NT Varenicline 1 mg T Placebo	124 129 124 129 121 Total: 627
Flexible Dosing Study A3051016 (nontreatment follow-up in A3051019)	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline flexible dosing 0.5 to 2 mg daily Placebo	 157 155 Total: 312
Long-term Safety StudyA3051037	52 weeks treatment	Varenicline, 1 mg BID Placebo	251 126 Total: 377
Study in Japan **A3051046_48**	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline 0.25 mg BID Varenicline 0.5 mg BID Varenicline 1 mg BID Placebo	153 155 156 154 Total: 618
Pivotal Study **A3051028**	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	349 329 344 Total: 1022
Pivotal Study **A3051036**	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	343 340 340 Total: 1023
Study in Taiwan and Korea **A3051045**	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	126 124 Total: 250
CV Disease Study **A3051049**	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	353 350 Total: 703
Multinational Asian Study **A3051055**	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	165 168 Total: 333

NPS=neuropsychiatric; BID=twice daily; CV=cardiovascular disease

a. Number of subjects=subjects randomized and treated, by treatment group and in total.

A meta-analysis of the psychiatric AEs reported in the 10 studies was conducted[101] and is described below.

10-Study Meta-Analysis Methods

All subjects who took at least 1 dose of the study drug (active or placebo) were included in the analysis; this included the 3091 varenicline subjects and 2005 placebo subjects. Incidence rates for psychiatric disorder AEs were summarized for varenicline (all doses) and placebo based on the pooled data from the 10 studies. The incidence rates for varenicline were compared with placebo using the RR from a Cochran-Mantel-Haenszel analysis and RD from a Mantel-Haenszel analysis, both using study as a stratification factor to account for any confounding due to interstudy differences, including unequal randomization ratios.[101] Respective nominal 95% CIs were calculated from these RR and RD point estimates. AEs were coded using the MedDRA version 11.0.

SAS version 9.0 (SAS Institute, Cary, NC, USA) was used for the analyses.

10-Study Meta-Analysis Results

An overview of AEs coding to the Psychiatric Disorders SOC by MedDRA HLGT is provided in Table 19. A higher percentage of varenicline subjects that reported any AE coding to the Psychiatric Disorders SOC than did placebo subjects (30.6% vs 20.8%), AEs related to sleep were the most frequent and were reported at a higher rate in varenicline than placebo subjects (25.1% vs 14.5%, respectively). However, the percentage of subjects reporting a psychiatric AE other than a sleep-related AE was similar in varenicline and placebo subjects (10.7% and 9.7%, respectively) with a RR of 1.02 (95% CI 0.86, 1.22) and a RD of 0.24% (95% CI 1.49, 1.96). Also, when only considering the subset of subjects reporting moderate and severe events (as rated by the Investigator) and considering any NPS events other than sleep-related events, the rates were similar for varenicline and placebo (4.9% and 4.0%, respectively with a RR of 1.11 (95% CI 0.85, 1.45).

Table 19. Incidence Rates and Risk Ratio of Psychiatric AEs by MedDRA HLGT in Placebo-Controlled Studies Completed Prior to 2009

Psychiatric disorders[a] (examples of PTs reported)	Varenicline (N=3091) (%)	Placebo (N=2005) (%)	Risk Ratio[b] (95% CI)
Any PT in the Psychiatric Disorders SOC	**946 (30.6)**	**418 (20.8)**	**1.43 (1.29, 1.58)**
Any PT in the Psychiatric Disorders SOC other than solely PTs in the sleep disorders and disturbances HLGT	**331 (10.7)**	**194 (9.7)**	**1.02 (0.86, 1.22)**
Adjustment disorders	0 (0.0)	1 (0.1)	NA
Anxiety disorders and symptoms	138 (4.5)	101 (5.0)	0.86 (0.67, 1.12)
Changes in physical activity (including restlessness)	33 (1.1)	20 (1.0)	0.76 (0.42, 1.39)
Cognitive and attention disorders and disturbances	0 (0.0)	1 (0.1)	NA
Communication disorders and disturbances	0 (0.0)	1 (0.1)	NA

Table 19. Incidence Rates and Risk Ratio of Psychiatric AEs by MedDRA HLGT in Placebo-Controlled Studies Completed Prior to 2009

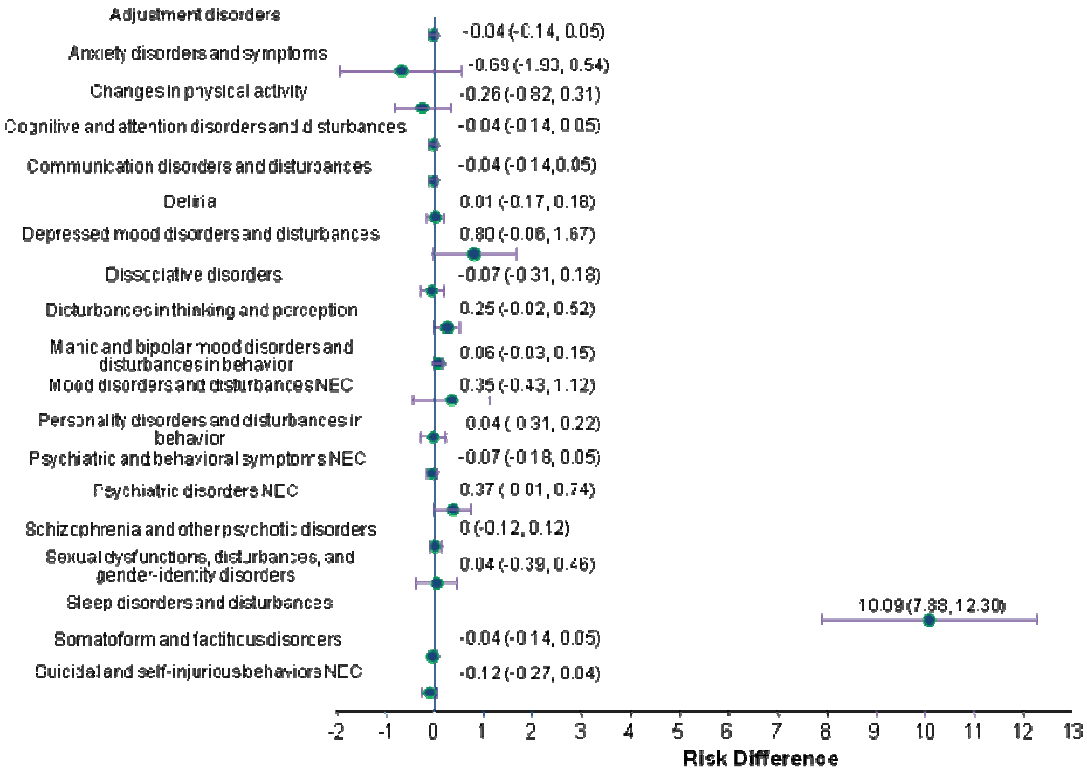
Psychiatric disorders[a] (examples of PTs reported)	Varenicline (N=3091) (%)	Placebo (N=2005) (%)	Risk Ratio[b] (95% CI)
Deliria (confusional state, disorientation)	3 (0.1)	2 (0.1)	1.07 (0.14, 8.12)
Depressed mood disorders and disturbances (including agitated depression, anhedonia, depressed mood, depression, depressive symptoms)	88 (2.8)	38 (1.9)	1.42 (0.96, 2.08)
Dissociative disorders	7 (0.2)	3 (0.2)	0.68 (0.18, 2.54)
Disturbances in thinking and perception (including hallucination)	13 (0.4)	2 (0.1)	3.29 (0.73, 14.81)
Manic and bipolar mood disorders and disturbances	2 (0.1)	0 (0.0)	NA
Mood disorders and disturbances NEC (including anger, apathy, frustration)	73 (2.4)	30 (1.5)	1.21 (0.79, 1.83)
Personality disorders and disturbances in behaviour (including aggression, hostility)	5 (0.2)	5 (0.2)	0.81 (0.21, 3.06)
Psychiatric and behavioural symptoms NEC (hypervigilance)	0 (0.0)	1 (0.1)	NA
Psychiatric disorders NEC (including nicotine dependence)	16 (0.5)	6 (0.3)	2.37 (0.91, 6.21)
Schizophrenia and other psychotic disorders	1 (<0.1)	1 (0.1)	0.99 (0.06, 15.74)
Sexual dysfunctions, disturbances and gender-identity disorders	18 (0.6)	10 (0.5)	1.07 (0.49, 2.34)
Sleep disorders and disturbances	776 (25.1)	291 (14.5)	1.70 (1.50, 1.92)
Somatoform and factitious disorders (conversion disorder)	0 (0.0)	1 (0.1)	NA
Suicidal and self-injurious behaviours NEC (suicidal ideation, suicide attempt)	0 (0.0)	2 (0.1)	NA

a. Subjects could have reported >1 psychiatric disorder, hence the sum of the incidence of individual psychiatric disorders does not equal the incidence of all psychiatric disorders.
b. Risk ratio estimates for varenicline vs placebo were stratified by study. Risk ratios were not calculated for high-level group terms with zero incidence in at least one treatment group.
MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; NEC = not elsewhere classified; CI = confidence interval.
Table adapted from Tonstad et al. 2010.
MedDRA version 11.0

The next most frequent types of psychiatric AEs after those coding to the Sleep disorders and disturbances HLGT were as follows: those coding to the Anxiety disorders and symptoms HLGT, which were reported at a slightly lower rate in varenicline than placebo subjects (4.5% vs 5.0%, respectively), those coding to the Depressed mood disorders and disturbances HLGT, which were reported at a higher rate in varenicline than placebo subjects (2.8% vs 1.9%), and those coding to the Mood disorders and disturbances NEC HLGT, which were reported at a higher rate in varenicline than placebo subjects (2.4% vs 1.5%). Anxiety, depressed mood and insomnia are common nicotine withdrawal symptoms as defined by DMS V[22]. Suicidal and self-injurious behaviors were reported only in 2 placebo subjects, 1 each reporting suicidal ideation and suicide attempt (intentional drug overdose).

The RDs and 95% CIs for each type of psychiatric AE for varenicline versus placebo are shown in Figure 25.

Figure 25. Risk Differences (95% CI) of Psychiatric AEs by MedDRA HLGT for Varenicline versus Placebo in Completed Placebo-Controlled Studies Prior to July 2009



The RDs for HLGTs in the Psychiatric Disorders SOC other than those related to sleep showed a small number of events, either in excess for placebo (up to 0.69 reported for Anxiety Disorders and Symptoms) or in excess for varenicline (up to 0.80 events reported for Depressed Mood Disorders and Disturbances). All these RDs were <1.00% and had associated 95% CIs including 0, indicating no significant difference for varenicline versus placebo. Multiple comparisons were conducted without a correction for multiplicity.

In summary, the analysis of NPS AEs in the 10 placebo-controlled Pfizer-sponsored varenicline studies completed prior to July 2009 showed that with the exception of sleep disorders and disturbances, NPS AEs were reported at similar and low (<5%) rates in both varenicline and placebo subjects. There was no evidence of an increased risk of NPS AEs, other than those coding to the Sleep disorders and disturbances HLGT, with varenicline treatment compared to placebo (RDs <1%, CIs including 0).

Appendix 6. Observational Studies

Appendix 6.1. Gunnell Study

Gunnell D, Irvine D, Wise L, Davies C, Martin RM. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. BMJ 2009;339:b3805.[102]

The Gunnell and Thomas publications were both conducted by researchers at the University of Bristol in the United Kingdom and were based on the same data source, per a grant received from the Medicines and Healthcare products Regulatory Agency. A brief description of the Gunnell publication is provided below.

Design: A cohort study based on the General Practice Research Database (subsequently known as the Clinical Practice Research Datalink) compared the risk of suicide and suicidal behavior in patients who took varenicline or bupropion to patients treated with NRT from 01Sep2006 to 31May2008.

Outcome: The primary outcomes were incident episodes of depression as measured by the date that antidepressant treatment was initiated and by fatal and non-fatal self harm as measured by death from suicide in the ONS mortality database and a hospital admission for self-harm that occurred within 3 months of the first prescription.

Results: This analysis included 63,265 patients prescribed NRT, 6,422 prescribed bupropion and 10,973 prescribed varenicline. In the fully adjusted model, the hazard ratio for fatal or non-fatal self harm was 1.12 (95% CI 0.67 to 1.88), for suicidal thoughts it was 1.43 (95% CI 0.53-3.85) and for start of antidepressant therapy it was 0.88 (95% CI 0.77-1.00) when varenicline was compared with NRT. There was no evidence that varenicline was associated with an increased risk of depression or suicidal thoughts.

For buproprion in a fully adjusted model, the hazard ratio for fatal or non-fatal self harm was 1.17 (95% CI 0.59 to 2.32), for suicidal thoughts it was 1.20 (95% CI 0.28-5.12) and for start of antidepressant therapy it was 0.91 (95% CI 0.77-1.07) when bupropion was compared with NRT.

Authors' Conclusion: Based on the confidence interval, although a two-fold increased risk of self harm with varenicline cannot be ruled out, these findings provide some reassurance concerning its association with suicidal behaviour.

Strengths and Limitations: There are several limitations to this analysis. First, study power was limited. Despite the large coverage of the database, the study identified only 10,973 people prescribed varenicline and only 18 episodes of self harm in this group. Second, the analysis is restricted to products prescribed in primary care. Patients receiving smoking cessation products in NHS smoking cessation clinics or buying over the counter products from pharmacies will be excluded. Third, people taking varenicline and bupropion may be more likely to have already tried (and failed) to stop smoking with NRT and so differ in underlying characteristics or level of addiction (and possibly suicide risk) compared with those prescribed NRT. Next, bupropion is licensed for the treatment of depression in some

countries (but not the UK). It is possible (though unlikely) that some bupropion prescribing is off-label use for depression, which would exaggerate any increased suicide risk associated with bupropion. Fifth, this is an observational study and the small differences (or lack of differences) between products could be due to uncontrolled confounding. Last, full death certificates were not obtained for study members who died, possibly leading to an underestimation of suicide deaths.

The strengths of this study included using the General Practice Research Database, which contains detailed records of prescribing and health related events for a large number of people registered with general practitioners in the UK.

Appendix 6.2. Population-Based Observational Studies – Power to Detect Increased Risk of NPS Events

The authors of the observational studies reviewed in Section 5.3.3.2.1 commented on the power of the studies to detect an increase in NPS risk. Thomas et al[50] indicated that an 80% power at a 5% level of statistical significance was needed to detect a 1.5-fold increase in risk of self harm with varenicline compared with other products. According to Meyer et al[52], due to the rarity of NPS hospitalizations (within 30 days), a much larger sample size (~2.5 million) would be needed to confirm a null association, and an even greater sample size to detect an increased risk of idiosyncratic reactions that occur at a rate <1 in 100,000 patients. Pasternak et al mentions the low power of the study to detect an increase in risk for suicide attempts and suicides.

Pfizer calculated the power to detect a HR of 1.5 or 2 (as referenced in Thomas et al[50]) for suicide/self-harm related endpoints or for the main composite NPS outcomes that include suicide-related events for varenicline versus comparator. No power calculations could be done for endpoints for which a HR was not reported.

The approximate power calculation was performed by using a normal distribution for the natural logarithm of the hazard ratio (Ln (HR)) and using the reported HR and its confidence interval to estimate the HR standard error.[103] The results are presented in Table 20 below.

Table 20. Observational Studies – Approximate Power[a] to Detect HR of 1.5 and 2 for NPS Events, Varenicline versus Comparator

Study	Endpoint	Model	Varenicline N	Comparator[b] N	HR Reported (95% CI)	Power to Detect HR of 1.5	Power to Detect HR of 2
Meyer et al 2013	**NPS hospitalization (30 days)**	Crude	19933	15867	0.57 (0.33-0.98)	31%	71%
		Propensity score matched	10 814	10 814	1.14 (0.56-2.34)	20%	47%
	Suicide attempts (30 days)[c]	Crude	19933	15867	0.20 (0.02- 1.78)	6%	9%
		Age and sex adjusted	19933	15867	0.18 (0.02-1.69)	5%	9%

Table 20. Observational Studies – Approximate Power[a] to Detect HR of 1.5 and 2 for NPS Events, Varenicline versus Comparator

Study	Endpoint	Model	Varenicline N	Comparator[b] N	HR Reported (95% CI)	Power to Detect HR of 1.5	Power to Detect HR of 2
VA study, unpublished	**NPS hospitalizations (30 days)**	Propensity score matched	14131	14131	0.76 (0.40-1.46)	23%	55%
Pasternak et al 2013	**NPS emergency visits or hospitalisations (30 days)**	Unmatched	59790	17936	0.69 (0.49 - 0.98)	62%	97%
		Propensity score matched	17935	17935	0.85 (0.55-1.30)	46%	89%
Thomas et al 2013	**Fatal and non-fatal self harm (3 months)**	Basic	30352	78407	0.70 (0.41-1.18)	33%	74%
		Fully adjusted	30352	78407	0.88 (0.52-1.49)	33%	73%

a. The approximate power calculation was performed by using a normal distribution for the Ln (HR) and using the reported HR and its confidence interval to estimate the HR standard error.
b. For Pasternak et al Comparator=Bupropion, for all other studies Control=NRT.
c. Suicide attempt data are from the full report obtained through the Freedom of Information Act[53].

As shown above, among the 4 observational studies reviewed, the Pasternak et al[54] study had sufficient power with both models used (89% and 97%) to detect a two-fold increase in the primary endpoint (NPS emergency visits or hospitalizations). Two of the other studies had almost sufficient power (>70%) to detect a 2-fold increase in the primary endpoint: Thomas et al[50] for Fatal and non-fatal self harm (both models used) and Meyer et al[52] for NPS hospitalization (crude model). The VA unpublished study, based on information available in the public domain, did not have sufficient power in the propensity score matched model to detect a 2-fold increase in the risk for the primary endpoint (no other data is available). The studies were underpowered to detect a 2-fold increase in other endpoints not shown in Table 20 or to detect a 1.5-fold increase in any of the endpoints included in the studies.

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